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The role of regulatory RNA elements in the structure, cellular functions and diseases of RNA: an update

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ABSTRACT

In nature, Ribonucleic acid (RNA) was believed to regulate RNA metabolism, function and modulate cellular processes of life. Recent advancements in Genomics and disease pathology have given insight on the aberrant modifications in RNA causing diseases in Humans such as autoimmune, neurodegenerative, cardiovascular diseases, suggesting that the structure, folding and regulatory roles of RNA are also important. Cis elements within the RNA and trans binding factors have several functional and regulatory roles. The regulatory elements such as miRNA, lncRNA, viral genomic RNA have potential downstream effects on RNA functions. The present review is to update the current knowledge of RNA regulation with its cis and trans elements. With background to the topic and types of cis elements, the second chapter in details describes the regulation of RNA through several mechanisms. Using example of drosophila, the coordinated regulation is described to highlight the mechanism and elements involved. Aberrant RNA structures in human diseases are described in the subsequent chapter. Finally, the therapeutic potential is discussed. The review thus highlights the architecture of RNA and its role in gene regulation and disease. The recent advancements in computational biology and drug discovery have highlighted the importance of the diverse structure and dynamics of RNA.

Keywords: *RNA cis-regulatory elements; RNA binding proteins; U-rich elements (ARE); Stem-loops (SL) structures: Riboswitches..*

1. Introduction

RNA, once thought to be merely a transmitter of genetic information, is now recognized as a versatile biomolecule that plays essential roles in gene regulation, viral and bacterial defense mechanisms, molecular scaffolding, and numerous cellular processes. RNA molecules can adopt complex structures and undergo significant conformational changes *in vivo*, enabling them to respond dynamically to cellular and environmental cues [14]. Moreover, a single RNA transcript may exist in multiple sequence isoforms and can exhibit dynamic structural rearrangements as well as diverse chemical modifications [11]. This remarkable structural and functional plasticity allows RNA to rapidly adapt to changing cellular environments and physiological conditions [23].

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Although certain RNAs can function independently, such as by influencing phase separation through RNA–RNA interactions [178], most cellular RNAs are extensively associated with proteins. The biological function and fate of an RNA molecule are ultimately determined by a finely regulated network of interactions with trans-acting partners, including proteins, DNA, and other RNA molecules. These binding partners execute their regulatory functions by recognizing RNA cis-regulatory elements in a sequence- and/or structure-specific manner, with RNA architecture frequently serving as a critical determinant of complex formation [152]. To interact efficiently with target RNA elements, RNA-binding proteins (RBPs) typically possess modular architectures composed of multiple RNA-binding domains (RBDs) and often engage in homo- or heterodimerization [156]. Such arrangements enhance both specificity and binding affinity by expanding the interaction interface between proteins and RNA molecules. Regulatory RNA elements control diverse biological processes, including translation, transcript abundance, RNA processing, and viral genome replication. The corresponding trans-acting factors bind these cis-elements and confer functionality to the resulting ribonucleoprotein (RNP) complexes. Importantly, the structural flexibility of RNA frequently contributes to the specificity and efficiency of RNP assembly [47]. The functional integrity of cis–trans regulatory interactions depends on the availability of correctly folded RNA structures and their ability to undergo controlled conformational transitions. Disruptions in these processes can lead to aberrant cellular functions and contribute to the development of numerous disease states. Therefore, understanding RNA structural organization and conformational landscapes is essential for elucidating mechanisms of gene regulation and cellular homeostasis.

One of the major challenges in molecular biology is the identification and characterization of regulatory RNA elements, particularly those embedded within dynamic regions that undergo chemical exchange and may remain inaccessible to conventional detection methods.

Recent advances in structural probing technologies have significantly improved our ability to investigate RNA structures within living cells, allowing the characterization of secondary and, to some extent, tertiary structures of medium- and large-sized RNAs *in vivo*. These developments have led to the emergence of four-dimensional (4D) RNA structural biology, an approach that monitors RNA structural changes throughout its life cycle in response to alterations in cellular environments and external stimuli [108]. Quantitative characterization of RNA structural ensembles is expected to reveal how disease-associated mutations and epitranscriptomic modifications influence RNA conformational equilibria, particularly within cis-regulatory regions that govern gene expression. In parallel, increasing attention has been directed toward intrinsically disordered regions (IDRs) and flexible linker segments within RNA-binding proteins. These regions are now recognized as important modulators of RNA-binding affinity and specificity [166]. Furthermore, variations in protein concentration, post-translational modifications, and post-transcriptional RNA modifications are anticipated to influence the composition, dynamics, and functionality of RNP complexes. This review aims to summarize current knowledge regarding the structural features, conformational dynamics, and regulatory elements that govern RNA function and stability. The first section provides an overview of the major classes of RNA regulatory elements. Subsequent sections discuss the mechanisms of RNA-mediated regulation and transient control of gene expression in detail. Finally, the review examines the involvement of RNA structural alterations in human diseases and highlights their potential as targets for therapeutic intervention and drug development.

2. Types of regulatory RNA elements

The finding that tiny transcripts, hitherto viewed as "junk," can serve critical roles as cellular regulators has stunned the RNA world. Regulatory RNA elements execute a variety of physiological operations, including gene silencing, translational regulation, transcript level control, viral genome replication regulation, mRNA degradation, and localization or integration of external stimuli. Furthermore, regulatory RNAs participate in key sensory activities and regulatory responses to environmental signals [88]. Although the initial so-called cis-regulatory elements, such as AU-rich elements (ARE) and mRNA start codons, were single-stranded, the discovery of trans-acting factors, such as RNA-binding proteins, bind them provided functionality to the complex. The presence of appropriately folded RNA elements is required for the functional integrity of cis-trans pairs, and several pathological states can occur from RNA conformational shifts [83]. Regulatory RNA elements can be found in the coding sequences and untranslated regions (UTRs) of mRNAs, lncRNAs, miRNAs, and viral genomic or subgenomic RNAs. The bulk of regulatory units interact only with the trans factors however elements can function in both cis and trans for potential RNA downstream effects [180]. Cell-based screening methods, computer analysis of genetic data, and predictions have all contributed to the discovery of RNA elements [188] & [65].

Linear *cis*-Elements

Unlike RNA cis-elements, cis-regulatory elements (CREs) in DNA are specific genomic regions that serve as binding sites for transcription factors (TFs). These regulatory sequences function as molecular switches that precisely control the dosage, timing, and spatial patterns of gene expression during development and cellular differentiation [106]. The systematic identification and characterization of CREs have greatly facilitated the annotation of functional non-coding regions of the genome, providing valuable insights into the organization of gene regulatory networks and the mechanisms governing target-site selection [36]. Among RNA regulatory elements, linear *cis*-elements were the first to be recognized and characterized. The availability of complete genome sequences has significantly accelerated the identification of *cis*-regulatory regions within potential target transcripts that are controlled by corresponding RNA-binding proteins (RBPs) or microRNAs (miRNAs) acting in trans [179]. These linear RNA elements mediate sequence-specific interactions with diverse trans-acting factors, including proteins, miRNAs, and long non-coding RNAs (lncRNAs). Conventional RNA-binding proteins generally recognize short sequence motifs ranging from 3 to 10 nucleotides, whereas miRNAs, typically 21–23 nucleotides in length, bind their target sites with high specificity through complementary base pairing [33].

RNA-binding proteins achieve enhanced specificity and affinity through their modular architecture, which often contains multiple RNA-binding domains (RBDs) capable of simultaneously interacting with clusters of linear RNA *cis*-elements [156]. Consequently, both proteins and regulatory RNAs utilize these linear motifs to recognize and regulate their target transcripts. Among the earliest identified RNA regulatory elements were AU-rich elements (AREs), which play crucial roles in controlling mRNA degradation and stability [133]. Similarly, the highly conserved 7-nucleotide miRNA seed sequence mediates accurate target recognition by Argonaute (AGO) proteins within the RNA-induced silencing complex (RISC) [25]. Although linear *cis*-elements are defined primarily by their nucleotide sequences, their biological functions are often strongly influenced by the surrounding RNA structural context. These motifs may be exposed or sequestered within secondary and tertiary RNA structures, thereby regulating their accessibility to trans-acting factors [87]. Consequently, structural embedding represents an additional layer of regulatory control beyond sequence recognition alone. While many RNA-binding proteins interact with linear motifs in a sequence-dependent manner, the structural environment surrounding these motifs is frequently essential for their functional activity [194]. A notable example is provided by the AU-rich and G-rich *cis*-elements present in *Trypanosoma cruzi*, which regulate developmental stage-specific mRNA stability through interactions with specialized RNA-binding proteins [80].

Stem-Loop *cis*-Elements

Stem-loops (SLs) are among the most common structural motifs in RNA and consist of paired stem regions interrupted by internal symmetric or asymmetric loops, bulges, and variable stem lengths [13]. Variations in stem length, loop composition, and branching patterns contribute significantly to the structural diversity and stability of RNA molecules. The formation of branched stem-loop architectures and their higher-order structural arrangements further expands the repertoire of RNA tertiary structures and regulatory functions [87].

Among the best-characterized stem-loop *cis*-elements are the alternative decay elements (ADEs) and constitutive decay elements (CDEs), which regulate mRNA turnover through interactions with the multidomain RNA-binding protein Roquin [18]. These elements typically contain hexa-loop or tri-loop structures that mediate sequence-specific recognition by Roquin within an overall structure-dependent binding framework. Interestingly, certain stem-loop elements such as CDEs can also function as AU-rich elements (AREs) when present in a linear conformation, thereby recruiting conventional ARE-binding proteins such as AUF1 and integrating multiple layers of post-transcriptional regulation [18].

Another important stem-loop regulatory motif is the Smaug recognition element (SRE), which facilitates translational repression and mRNA degradation through sequence-specific recognition within a hairpin structure [129]. Stem-loop elements are also involved in translational regulation during the life cycle of various parasites, including *Leishmania*, where they contribute to developmental stage-specific gene expression control [38]. Furthermore, RNA localization signals, commonly referred to as "zip codes," frequently adopt stem-loop conformations that determine the intracellular destination of mRNAs and enable spatial regulation of translation. These structures are often recognized by double-stranded RNA-binding proteins that mediate RNA transport and localization [75]. Additional examples of functional stem-loop elements include iron-responsive elements involved in cellular iron homeostasis and viral packaging signals that regulate genome encapsidation and replication [70].

Cis-Elements with Higher-Order Structures

Beyond simple stem-loop motifs, many RNA regulatory elements adopt complex higher-order structures composed of interconnected stem-loops, bulges, junctions, and single-stranded regions. The modular organization of RNA frequently requires the sequential folding of individual structural domains, which subsequently interact through long-range tertiary contacts to generate functional architectures [157]. Such higher-order structures play critical roles in regulating RNA stability, translation, and interactions with proteins and other nucleic acids. Pseudoknots represent one of the most extensively studied classes of higher-order RNA structures. These motifs are formed when nucleotides within a loop region base-pair with a complementary single-stranded sequence located elsewhere in the molecule. Viral frameshifting elements (FSEs) are notable examples of pseudoknot-containing structures that regulate programmed ribosomal frameshifting during translation [21]. Another important class of highly structured RNA elements is exoribonuclease-resistant RNAs (xrRNAs), which are found in numerous viral genomes. These elements achieve remarkable resistance to nuclease degradation through exceptionally stable tertiary structures formed by pseudoknot interactions that generate a protective ring-like architecture around the RNA molecule [163]. This structural arrangement effectively blocks the progression of 5′→3′ exoribonucleases and contributes to viral RNA stability and persistence.

Internal ribosome entry sites (IRESs) provide another example of complex RNA structural elements. These motifs frequently mimic transfer RNA (tRNA)-like architectures and facilitate cap-independent translation initiation, enabling protein synthesis under conditions where canonical translation mechanisms are impaired [51].

The activity of IRES elements is regulated by several RNA-binding proteins. For example, the proteins HuR and HuD negatively regulate IRES-mediated translation by inhibiting ribosomal recruitment [51]. In contrast, polypyrimidine tract-binding protein 1 (PTBP1) enhances IRES function by stabilizing the RNA in a ribosome-compatible conformation and recognizing consensus sequences within a structured RNA environment [172]. Higher-order RNA structures also include G-quadruplexes, which are specialized guanine-rich conformations involved in the regulation of RNA metabolism and gene expression. The biological significance of these structures is highlighted by observations that mutations affecting G-quadruplex-binding proteins can contribute to disease pathogenesis. For instance, a point mutation in TAR DNA-binding protein 43 (TDP-43), frequently identified in patients with amyotrophic lateral sclerosis (ALS), markedly reduces its affinity for G-quadruplex structures, potentially disrupting normal RNA regulatory processes [198].

Discontinuous *cis*-Elements

Discontinuous *cis*-elements represent a distinct class of regulatory RNA elements in which two or more spatially separated sequence regions interact to form a functional structural unit [60]. Unlike linear regulatory motifs, these elements are composed of distant RNA segments that are brought into close proximity through RNA folding and long-range intramolecular interactions. Such interactions can span hundreds or even thousands of nucleotides, thereby enabling communication between distant regions of an RNA molecule and contributing to the regulation of diverse biological processes.

Long-range RNA–RNA interactions are particularly prevalent in viral genomes, where they play essential roles in coordinating replication, translation, and genome packaging. Members of the *Flaviviridae* family and several other viral taxa extensively utilize intramolecular long-range interactions to regulate genome replication and maintain structural integrity [106]. In many flaviviruses, complementary sequences located within highly structured regions at the 5′ and 3′ termini interact with one another, resulting in cyclization of the viral RNA genome. This circularized conformation is critical for efficient replication because it promotes the activity of the viral RNA-dependent RNA polymerase (RdRP), thereby enhancing viral RNA synthesis [185], long-range RNA interactions are frequently employed by viruses to regulate translation. These interactions allow distant regulatory elements to communicate and coordinate translational control across the viral genome. A well-characterized example is found in the *Pea enation mosaic virus* (PEMV), where a T-shaped RNA *cis*-element located at the 5′ end of the viral genome interacts with a stem-loop structure situated within the coding region through a kissing-loop interaction [63]. This long-range structural communication facilitates efficient translation and highlights the importance of discontinuous *cis*-elements in viral gene expression. Because it interacts with ribosomal subunits, this newly discovered element is required for increased viral protein translation. Two hairpins from the Barley yellow dwarf virus (BYDV) 5′ and 3′ UTRs have been hypothesized to create a kissing-loop interaction that regulates ribosome access to the translation initiation site [145]. As a result, the interaction regulates the translation pace by constantly forming and breaking down structures. Figure 1 depicts the many types of RNA cis-regulatory elements and their cellular roles.

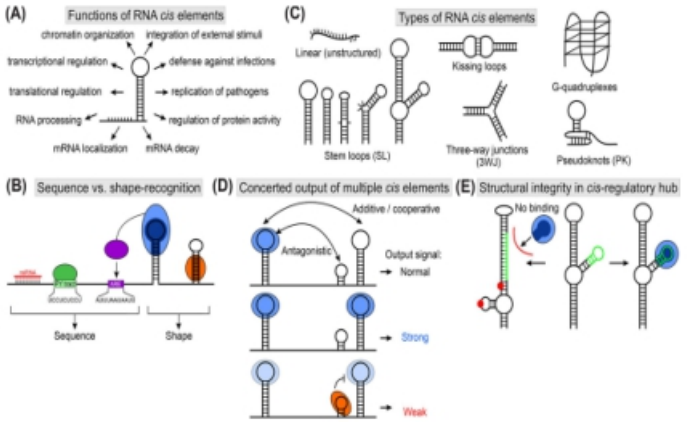

Figure 1: Illustration of types and function of RNA cis-regulatory elements. Tants and Schlundt. Bioscience Reports (2024)

3. Regulatory and transient elements in RNA and their role in RNA conformation

RNA, once thought to be just a transmitter of genetic information, is now recognized as a versatile biomolecule that regulates gene expression [120], microbial defense mechanisms [144], and scaffolding [120]. RNA can acquire complex structures and exhibit significant structural changes as a result of active unfolding *in vivo*. Large RNA molecules have distinct three-dimensional structures due to extensive tertiary interactions [104]. Large RNA molecules have a relatively flat overall form and are made up of stacked layers of a near-planar arrangement of contiguous coaxial helices [165]. A diversified variety of tertiary interaction motifs stabilize the functional core of these structures, often bringing together distant areas of conserved nucleotides [39]. Furthermore, a single RNA molecule can exist in many sequence isoforms or have a dynamic structure and level of alteration [83]. This variety and plasticity enable quick adaptation to changing cellular environments. Eukaryotic 5' UTRs frequently switch between conformations in a dynamic equilibrium [105]. Depending on the cellular environment, mRNA can switch between a structured, inaccessible state (which inhibits translation) and a relaxed, single-stranded state [59].

In vitro examination of cis-element interplay demonstrates how multi-domain proteins simultaneous binding of two RNA elements integrates sequence and shape recognition to improve target search selectivity. This cooperative contact produces a "threshold" or "switch-like" effect [19]. Furthermore, it guarantees that target transcripts are only suppressed when microRNA concentrations reach a predetermined threshold, eliminating unpredictable swings and fine-tuning cellular responses. The switch effect is illustrated in *C.elegans* by the regulation of target mRNA degradation by let-7 and lin-4 miRNAs [58]. Cold Shock Domain-Containing Protein E1 (CSDE1, or UNR) regulates translation by identifying and interacting with particular RNA structures in the 5' Untranslated Region (UTR) [68]. By determining whether the 5' UTR folds into an active Internal Ribosome Entry Site (IRES) or an inhibitory stem-loop, CSDE1 functions as an RNA chaperone, dynamically regulating translation [30]. Helicases and point mutations can influence the conformational ensemble by stabilizing or destabilizing individual conformations, altering the equilibrium and adjusting translation efficiency [101] and [62]. The ultra-conserved 5' UTR elements provide multiple RNA structures for cell type-specific and fine-tuned gene expression regulation [182].

The dimmer switch precisely fine-tunes and regulates the dynamic range of protein expression and non-canonical translation across cell types and developmental stages. The two mechanisms Steric blocks and Helicase targets enable alternative conformation structure-dependent switches which function as a structural rheostat [113] and [93].

Cis-Elements and Their Role in RNA Conformation

RNA regulatory functions are often mediated through multiple copies of the same *cis*-regulatory element or through structurally redundant variants that produce additive or synergistic effects on gene regulation [177, 135, 136]. The presence of multiple regulatory elements within a single transcript enhances the robustness of RNA-mediated regulation by minimizing the impact of mutation-induced perturbations and enabling precise modulation of gene expression outputs. Such regulatory architectures provide both functional redundancy and flexibility, ensuring reliable biological responses under varying cellular conditions.

A well-characterized example is the *ASH1* mRNA of budding yeast, whose localization to the bud tip is mediated by four distinct localization elements. Remarkably, each of these elements is individually capable of directing proper localization, demonstrating the redundant yet cooperative nature of RNA regulatory motifs [160]. Similarly, multiple *cis*-elements can function together to coordinate regulatory outcomes, as observed in transcripts containing several microRNA response elements. The cooperative action of these elements enhances the efficiency and specificity of post-transcriptional regulation. An example is the regulation of the Whi3 protein, which contains a long intrinsically disordered polyglutamine (polyQ) tract and whose expression is influenced by multiple interacting regulatory elements [182]. Structured RNA elements can also exhibit cooperative behavior through the coordinated recruitment of multiple trans-acting factors. For instance, Essig and colleagues demonstrated that the binding of several Roquin molecules to six spatially separated stem-loop structures within the 3′ untranslated region (UTR) of *Nfκb* mRNA occurs cooperatively, thereby enhancing post-transcriptional regulation [52]. Such cooperative interactions enable regulatory complexes to integrate signals from multiple RNA motifs and generate finely tuned biological responses.

In *Caenorhabditis elegans*, regulation of the transcription factor *die-1* provides another example of combinatorial control mediated by multiple *cis*-elements. Downregulation through the 3′ UTR is achieved via partially additive and redundant regulatory mechanisms that contribute to the establishment of left–right asymmetry in gustatory neurons [138]. These observations highlight how multiple regulatory elements can collectively ensure precise developmental and physiological outcomes. Importantly, not all *cis*-elements participate directly in the binding of trans-acting factors. Some elements serve structural roles by maintaining the overall architecture of regulatory hubs and preserving the optimal spatial arrangement of functional binding sites. Such structural elements are essential for proper RNA folding and the formation of higher-order conformations that facilitate efficient regulatory interactions. A notable example is the alternative splicing of the *Drosophila Dscam* gene, which encodes a cell-adhesion molecule crucial for neuronal wiring and immune responses. In this system, long-range RNA structural interactions contribute to the accurate selection of alternative exons, demonstrating how RNA conformation itself can act as a regulatory determinant [66].

Collectively, these examples illustrate that *cis*-elements function not only as individual recognition motifs but also as integral components of complex structural and regulatory networks. Through redundancy, cooperativity, and architectural organization, *cis*-elements shape RNA conformations that are essential for precise control of localization, stability, translation, and alternative splicing.

Structural changes

Tetraloops, ribozymes, and riboswitches are examples of stiff protein-like structures formed by different RNA folds [103]. This structural stiffness is necessary for a wide range of cellular operations. Secondary structures (such as hairpins and stems) form quickly and act as strong architectural scaffolds [20]. Tertiary contacts, such as pseudoknots or coaxial stacking, then lock the RNA in specific functional states [142]. This sequential process substantially limits the number of potential conformations. Most RNAs, however, sample numerous conformations in a dynamic, rather than random-equilibrium, manner. RNA folding takes place on a rough free-energy landscape. Rather than diffusing randomly, the molecule moves between defined local minima (structural states) separated by precise energy barriers [168]. These changes can be intrinsic if several structures are stabilized by a common free enthalpy. These transitions function as molecular switches. Specific conformational changes are frequently associated with diverse functional states, allowing the RNA to respond to environmental stimuli, bind ligands, and interact with proteins in a highly regulated, non-random manner [176] and [99].

Temperature, pH, and ligand binding can all cause structural changes. Temperature can destroy hydrogen bonds in hairpins and stems, as well as melt inhibitory RNA structures. RNA thermoswitches are used by bacteria to modulate the expression of virulence genes in response to environmental changes [111]. pH alters the protonation states of specific nucleotides, particularly adenine and cytosine bases, while also forming new hydrogen bonds [16]. Also, pH causes the RNA to fold into a completely different three-dimensional structure. Ribozyme catalysis is an example of this form of folding [3]. Certain small molecules, metabolites, or ions (Mg2) bind to an untranslated portion of the RNA. This interaction stabilizes a specific tertiary structure, frequently trapping the RNA in an "on" or "off" state, promoting or terminating gene expression. One example is the Mg2+-dependent glmS riboswitch, which functions as both a metabolite sensor and a catalytic RNA [91]. Mutations can cause changes in RNA folding by modifying (distant) base-pairing patterns.

The switch in 3′ Splice Site Recognition between exon definition and splicing catalysis is critical for Drosophila sex-lethal autoregulation, and recent research has shed light on structural and stability alterations in RNAs caused by mutations such as m6A. Trans factors (RNA-binding proteins, transcription factors, and initiation factors) can cause significant structural changes when bind [73]. The two methods are structural flexibility to bind specific target sequences, causing local or global conformational changes [57] and melting of double-stranded structures or exposing previously masked single-stranded areas [147]. Trans factors influence RNA interactions. Rather than simply recognizing DNA sequences, many TFs use specialized domains to bind nascent RNAs produced at active transcription sites as modulate gene regulation through chromatin localization, transcription control and post-translational fate [130].

Dynamic conformational transitions

Dynamic transitions between several conformations enable RNA to respond to and assimilate various stimuli [83]. The key mechanisms that enable this function include structural plasticity, stimulus integration, and functional states [131]. Structural plasticity is facilitated by subtle shifts in the sugar-phosphate backbone that allow for structural adaptation at protein-binding interfaces [162] and alternative base-pairing motifs such as "k-turns" that can switch between different conformational states (e.g., N1 and N3 classes) depending on environmental context [77]. Epitranscriptomic changes such as A-to-I editing and pseudouridine have a direct impact on base pairing, altering RNA reactivity and RBP affinity [109]. Because RNA folds during synthesis, upstream nascent sequences interact with flanking regions and respond to local signals in real time, changing the energetic folding pathway [153].

Dynamic changes between structural states are required for RNA functionality. To allow viral transactivation, the HIV TAR element must shift into a stacked conformation stabilized by a base-triple [26]. Similarly, "riboswitches" are functional RNA structures that physically change shape when bind to a target molecule, thereby turning genes on or off by hiding or exposing start codons [151]. Long non-coding RNAs (lncRNAs) are one example of molecular scaffolds that change conformations to connect with a variety of proteins. Few example- exemplifying the mRNA structures change during development and infection are the 5' hairpin of 7SK RNA which was experimentally shown to exist in four distinct conformations, of which only one stable state could interact with the protein HEXIM [150], and the FSE of SARS-CoV-2 (the virus causing coronavirus disease in 2019 (COVID-19), with varying effectiveness in frameshifting through altered binding to ribosome [154].

Trans- binding proteins

RNA scanning selects trans-binding partners (such as proteins, microRNAs, or other RNAs) and regulates its own shape in a dynamic process. For example, during splicing, hnRNP U and hnRNP L attach to the identical SL region in the MALT1 mRNA, but with opposing consequences [87]. hnRNP U increases the stability of the structured RNA, whereas hnRNP L unfolds the element and exposes a second trans factor binding site, resulting in exon inclusion and alternative splicing via engagement of U2AF 1 and U1 snRNP. Once bind, the interaction can cause additional structural modifications, locking both the RNA and its partner into a tightly stabilized, functioning complex using the Induced Fit mechanism. Hfq dynamically bind to RNA, promoting local unfolding so the RNA can "explore" other conformations and successfully locate the correct trans-binding partner [6]. Because RNA transcribes and folds concurrently, it often forms alternative secondary or tertiary structures (e.g., hairpin loops vs. extended structures like G-quadruplexes) [185].

Roles in miRNA-mediated functions

Regulation of trans factor binding sites is an important aspect of RNA structure and the rate-limiting step in miRNA-mediated mRNA cleavage [123]. Trans-acting RBPs influence the rate of this pathway by either recruiting more repressive factors or shielding the mRNA from miRISC, hence determining how quickly deadenylation happens. RNA-binding proteins (RBPs) are essential trans-acting factors [34].

They bind to the 3'-UTR of the target mRNA and act as rate regulators, either by preventing the miRNA-induced silencing complex (miRISC) from accessing the binding site [164] or by inducing conformational changes in the mRNA that allow access to the target site [79]. Trans-acting RBPs dictate the speed of this pathway by either recruiting additional repressive factors or protecting the mRNA from miRISC, thereby controlling how fast deadenylation occurs [74].

Conformation changes enabling mimicry in Viruses.

Because they lack the equipment to generate their own proteins, viruses typically employ transfer RNA (tRNA) to hack host ribosomes [97]. tRNA-like Structures (TLSs) found at the 3' ends of many viral genomes fold into the typical L-shaped 3D form of canonical tRNA, allowing them to deceive host enzymes into "charging" the viral RNA with an amino acid [69]. Viral structures that imitate tRNAs can easily interact with important host translation factors, such as eukaryotic elongation factor 1A (eEF1A), to secure host resources for viral protein synthesis [9].

Internal structural domains globally resemble the shape of a full tRNA. This shape-mimicry enables the viral mRNA to latch directly into the ribosome's reading sites, controlling how the genetic information is read [22].

Changes in RNA structure frequently function as a molecular switch, changing RNA conformations in response to biological inputs. This shape-shifting capacity, seen in both non-coding and messenger RNAs, affects essential processes such as gene expression [184], splicing [110], and translation [40] without affecting the underlying genetic code. Thermosensors are RNA structures that melt or refold at specified temperatures, enabling organisms to regulate gene expression in response to environmental changes. During infection with *Vibrio cholera*, a temperature increase in the human host exposes the Shine Dalgarno (SD) sequence within an RNA thermometer structure [159]. Table-1 is a summary of cis RNA and their structure-function relationships.

Table 1: Types of cis RNA and their structure-function relationships

RNA element	Species	Structure	Interaction partner	Function	Associated disease/Refs
5 splice site	Eukaryotes	Linear	U1, U4, U5, U6 snRNP	Marks exon/intron boundary	Familial dysautonomia/ Anderson et al., 2001.
3 splice site	Eukaryotes	Linear	U2 snRNP	Marks intron/exon boundary	Gastrointestinal tumors/ Corless et al., 2004
Polypyrimidine tract (PPT)	Eukaryotes	Linear	U2AF65	Recruitment of further spliceosomal factors to 3 splice site	Tetrahydrobiopterin deficiency/ Meili, et al., 2009
Splicing enhancer/ silencer	Eukaryotes	Linear	SR proteins/ SR proteins, hnRNPs	Promotes exon inclusion/ exon skipping	Myeloma, type-2 diabetes/ Myeloma, infant mortality. Ogiya, et al., 2023; Hua, Yet al., 2008.
miRNA target	Eukaryotes	Linear	miRNAs	Translational regulation, mRNA decay	Viral infections, cancer/ 2 Kao, S.H et al., 2019
AU-rich element (ARE)	All kingdoms of life	Linear / (diverse)	AUF1 (HNRNPD), HuR (ELAVL1), TIA1, TIAR	Mediate mRNA decay for post-transcriptional control	Cancer, autoimmune diseases, infections. Tian, et al., 2020
Internal ribosomal entry site (IRES)	Viruses, eukaryotes	Multiple stem-loops	Ribosome, IRES-trans acting factors (ITAFs)	Cap-independent translation	Viral infections, cancer. Yang, Y., et al., 2018
Iron-responsive element (IRE	Eukaryotes	Stem-loop	Iron response protein	Modulates translation of genes involved in iron metabolism	Hyperferritinemia cataract syndrome. Halvorsen, et al., 2020
RNA thermometers and thermosensors	Eukaryotes, bacteria	Stem-loop	Ribosome, eEIF1A	Temperature-dependent control of gene expression	Bacterial infections. Weber, et al., 204.
G-quadruplexes	All kingdoms of life	Layers of G-quartets	TDP-43, FMRP	Translational regulation	Infections, neurodegenerative disorders, cancer. Liu, G., et al., 2022
Conserved RNA replication element (CRE)	Viruses	Stem-loop (14-nt loop)	3Dpol unit of replicase complex	Mediates replication of viral genome	Infections with enteroviruses and rhinoviruses. Cordey, et al., 2008

4. Co-ordinated translation regulation of RNA elements.

Lin [115] identified translational control as a critical regulatory mechanism for the flow of genetic information to produce proteomes and the primary way for regulating gene expression. Translational control, which governs mRNA effectiveness, influences the expression of several genes that respond to endogenous or external stimuli such as nutritional intake, hormones, or stress [146]. The bulk of eukaryotic mRNAs have relatively short half-lives (2h), hence changing their mRNA translational efficiency and protein degradation rates is required to rapidly change the cellular levels of the proteins they encode [49]. Initially surprising, mRNAs must now be viewed as structured, nonlinear arrays of numerous cis-acting components that span the whole message, primarily in the 5' and 3' untranslated regions (UTRs) [61]. mRNAs must be explored as messenger ribonucleoprotein particles (mRNPs), as their interaction with trans-acting factors is similar [92].

Translational results that integrate diverse signals via the corresponding trans-acting factors can be generated by combining miRNA binding sites or regulatory RBPs on specific mRNAs [94].

Almost all trans-acting factors bind to a variety of mRNAs that commonly encode functionally comparable proteins, resulting in coordinated, operon-like regulation [29]. This is a supplementary notion. Finally, RNA editing or modification (such as methylation) can provide an extra level of regulatory intervention for cis-acting regions. Translational control is at the heart of modern systems biology, thanks to the advent of techniques that enable highly parallel transcriptome-wide study of mRNAs and RBPs. Biological roles include bypassing nuclear transcription and RNA processing in order to effect practically instantaneous proteome alterations [2]. Translational control allows for the local production of proteins in specific cellular compartments, such as neuronal dendrites [1]. This regulation quickly inhibits the production of high-energy proteins during hypoxia or food restriction [17].

Oncogenesis, neurodegeneration, and metabolic disorders are all directly caused by dysregulation of the control mechanism [85]. The coordinated translation control of RNA elements is explained in the following two paragraphs with two examples. We discuss the distinctive events using Gebauer 2012 as a reference.

1. Combinatorial regulation, a multifunctional rbp, and tight translational repression: msl2 mRNA.

To inhibit msl2, the female-specific RBP Sex-lethal (SXL) works with two posttranscriptional regulatory mechanisms [116]. SXL suppresses the splicing of a short facultative intron in the msl2 5' UTR by binding to oligo-uridine segments in the nucleus; this splicing inhibition preserves the SXL-binding sites in the mature Mrna [90]. SXL suppresses msl2 translation in the cytoplasm by interacting with particular locations in the 3' UTR and retained intron. Comprehensive mutational and functional investigations demonstrate that SXL modulates translation through two different mechanisms: While SXL combined with the 5' UTR precludes the scanning of complexes that have probably eluded the 3'-UTR-mediated regulation: SXL bind to the 3' UTR stops the 43S ribosomal complex from recruiting to the mRNA. By scanning 43S complexes, SXL assists in identifying the upstream initiator AUG and preventing them from reaching the main ORF. Despite binding to the same locations with similar apparent affinities, the highly conserved SXL homolog from *Musca domestica* does not inhibit translation, indicating that SXL, the msl2 3' UTR, and other elements required for repression interact specifically [8]. One of the major components was identified as the protein Upstream of N-ras (UNR), a conserved regulator recognized for its function in IRES-mediated translation and mRNA stability control in mammals. UNR is required for the *in vitro* translational suppression of msl2 reporters. Even if UNR is present in males, the absence of SXL prevents UNR from binding to msl2 and suppressing translation, as UNR requires SXL to bind to msl2's 3' UTR. As a result, SXL assigns a sex-specific role to UNR. This stimulation is thought to result from interactions between UNR and poly(A) tail-bind PABP. When PABP binds to the poly(A) tail and interacts with the cap-binding complex, the mRNA assumes a closed-loop structure that is thought to be ideal for effective ribosome recruitment. UNR has no effect on the closed-loop synthesis of msl2 mRNA, demonstrating that the SXL-UNR complex targets a translation initiation step downstream of eIF4F binding to inhibit ribosome recruitment. The presence of other components in the complete 3'-UTR repressor complex is indicated by a thorough examination of the msl2 3' UTR, which identifies areas required for translational repression but not required for SXL–UNR binding. Novel insights into how the SXL/UNR-organized complex on the 3'UTR of the msl2 mRNA regulates ribosome recruitment may be obtained by comprehending the makeup of this complex and how its constituent parts interact with the translational machinery. Figure-2 illustrates the mechanism of translational repression of msl2 mRNA.

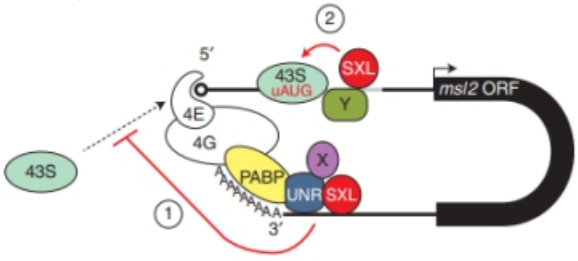

Figure 2: Mechanism of translational repression of msl2 mRNA. Gebauer et al., Cold Spring Harbor Perspectives in Biology .2012.

2. Nanos mRNA and its complex temporal and spatial control of translation

In the early phases of Drosophila development, the posterior determinant Nanos (Nos) is required for the formation of abdominal segments. The localization and translational activation of the Nos transcript at this site, along with translational inhibition elsewhere, allows for Nos synthesis to occur exclusively in the embryo's posterior [117]. Nurse cells actively translate and transcribe Nos mRNA before transporting it to the surrounding developing oocyte via ring canals. The translational control element (TCE), a unique region of the 3' UTR near the stop codon, comprises sequences that restrict the translation of Nos mRNA in the cytoplasm of late oocytes and early embryos [24]. The TCE is made up of three stem loops that are necessary for repression. To suppress translation in oocytes, the AU-rich stem of one of these structures (stem IIIA, as designated by Crucs [35]) must connect to the hnRNP F/H protein Glorund. Smaug recognition elements (SREs) are loops of CUGGC on the other two stems that are identified by the repressor Smaug [140]. Smaug, which is only expressed in the early embryo, controls the degradation of maternal mRNA during egg activation [158]. Point mutations in the SREs disrupt Smaug binding by triggering Nos suppression in the embryo, without affecting mRNA localization [140]. Smaug binds to the SRE via the SAM (sterile a motif) domain [143]. SAM domain recognition requires a core guanine in the SRE that is properly orientated by the stem-loop structure. Smaug recruits the CAF-CCR4-NOT complex to help in the de-adenylation of Nos RNA. Even though de-adenylation is required for Nos repression, deadenylated Nos reporters can still be significantly repressed in vitro in a way that is somewhat dependent on the SREs. These findings show that Smaug-mediated repression is divided into two parts: one independent of the poly(A) tail and one dependent on de-adenylation. Translational repression, which helps the repressed state, is frequently connected to de-adenylation.

Smaug interacts with Cup, a protein that binds to eIF4E and prevents eIF4G from forming the cap complex. Mutation of Cup's eIF4E-binding domains somewhat alleviates Nos transgene suppression, and the binding of Cup and eIF4G to Nos mRNPs is mutually exclusive, implying that Cup mediates Smaug's translation initiation block. Even when mRNA is completely unlocalized, early embryos form connections with polysomes. The absence of the Nos protein impairs the post-initiation phase. The Cricket paralysis virus (CrPV) IRES, which promotes translation initiation without the need for cellular initiation factors, has the potential to reliably block SRE-mediated translation. Thus, Smaug's repression could include both initiation and post-initiation processes.

Interestingly, new findings demonstrate that Cup can promote translational repression regardless of its eIF4E-binding motifs and can directly increase de-adenylation by interacting with the CAF-CCR4-NOT complex. This suggests that Cup may mediate Smaug's repressor effects via mechanisms other than translation initiation. Late ovarian extracts have recently been prepared to duplicate the repression caused by the IIIA stem (the Glorund-binding site). Repression appears to be cap-independent in these sequences. Furthermore, Glorund is detected in polysomes harboring the repressed mRNA, and polysomes are linked to Nos mRNA, implying that Glorund inhibits translation at the post-initiation stage. However, suppression in late oocytes is poly(A) dependent, which suggests that Glorund influences initiation.

When the polysomal association of Nos mRNA in total ovary extracts—which are enriched for early-stage oocytes—is compared to that in late ovary and embryo extracts, it gradually shifts to lighter fractions, which is consistent with the temporal acquisition of different mechanisms of translational repression. Figure-3 illustrates the mechanism of translational repression of nanos mRNA.

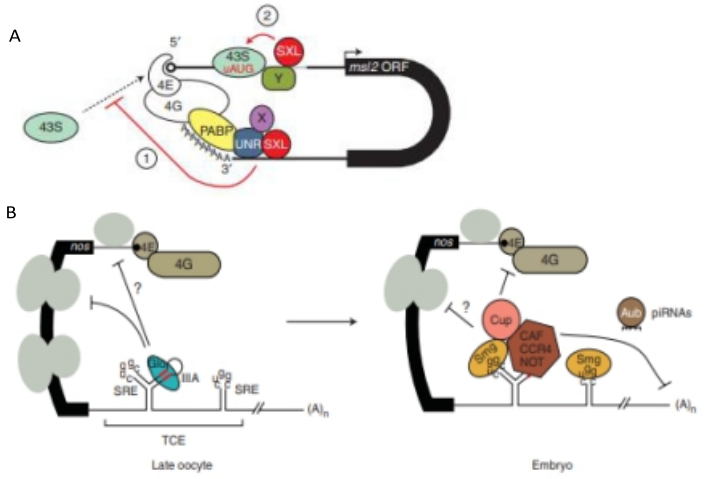

Figure 3: Mechanism of translational repression of nanos mRNA. Gebauer et al., Cold Spring Harbor Perspectives in Biology 2012

5. The role of RNA elements in Human Diseases

RNA plays an important part in many aspects of life due to its diverse structure and interactions with different proteins. Disruption of these connections causes disease genesis, including cancer, autoimmune, neurodegenerative illnesses, miRNA, and infections [167]. Changes in RNA's secondary structure generate differences in biological functioning due to point mutations, insertions, and deletions. Alternative splicing, as well as transcriptional and translational regulation, results in altered RNA structures, which have the potential to cause disease development. Figure-4 depicts the way of action of regulatory RNA through interactions, which may have implications for illnesses. In the next paragraphs, we will use examples to discuss mechanisms in various diseases. In neurological illnesses such as Huntington's disease, r(CAG) repeat expansion creates hairpin loops in exon 1 of the HD gene via lengthy tandem repetitions [86]. These are transformed into polyglutamine tracts, which produce toxic mass in neurons. RNA toxicity causes aberrant r(CAG) splicing, which leads to development of disease [173].

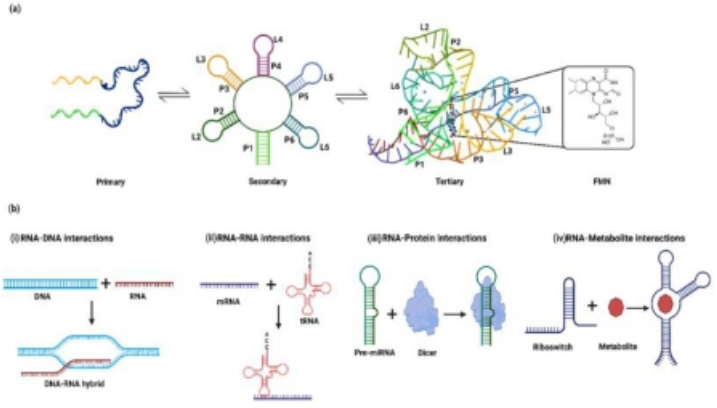

Figure 4: Mode of action of regulatory RNA via interactions: implications for diseases

In mRNA, methyl adenosine alteration at the N6 position causes changes in localization, splicing, stability, and translational regulation. M6A proteins, regulate target RNA and neuronal development in neurodegenerative illnesses such as Huntington's disease [86]. In Myotonic dystrophy type 1 (DM-1), r(CUG) repeat expansion leads to abnormal splicing of the insulin receptor (IR) and cardiac troponin T (cTNT) genes [173]. Research has shown that r(CAG)/r(CUG) is associated with numerous forms of spinocerebellar ataxias [86]. Mislocalization of TAR DNA binding protein 43 (TDP 43) causes irreversible neuron loss and gliosis in age-related neurodegenerative illnesses such as Parkinson's disease (PD) and Alzheimer's disease (AD) [173]. miRNAs are non-coding RNAs of 18-25 nucleotides that are initially transcribed by RNA polymerase II and then cleaved sequentially; miRNAs influence genes post-transcriptionally [121]. miRNA dysregulation contributes to neurodegeneration via dicer production, which leads to Amyotrophic lateral sclerosis (ALS) pathogenesis [46].

Other evidence includes mutations in tRNA biogenesis caused by *CLP1* gene mutations, which result in progressive brain atrophy and microcephaly in individuals. The silent mutation in the *tau* gene at the 5' exon splice site increases exon inclusion and destabilizes the stem loop with antisense RNA, resulting in PD pathology [28]. Spin cerebral ataxia type 10 is caused by an AUUCU repeat formed during the insertion of ALU elements such as LINE 1 [83]. Abnormal RNA modification (changes in CD4+ T cells) in peripheral blood, tissues, and cells promotes autoimmune disease progression [78]. The alteration of m6A proteins controls systemic lupus erythematous (SLE) [68]. According to research, the mRNA levels of *METTL3*, *WTAP*, *ALKBH5*, *FTO*, and *YTHDF2* genes are much lower in diseased persons. METTL3, ALKBH5, and YTHDA1 mRNA levels are higher in T cells, while ALKBH5, RBMX, RBM15B, and YTHDF1 mRNA levels are lower in peripheral blood. As a result, it is clear that in the case of auto immune illnesses, mRNA modification-related enzymes are either increased or downregulated, leading to disease progression. In rheumatoid arthritis, gene expression of *ALKBH5* and *FTO* genes are increased, facilitating m6A modification while negatively regulating migration, invasion, and proliferation [41]. According to research, the genes *IGF2BP1* and *IGF2BP2* are downregulated in Crohn's disease tissues [177].

Abnormal gene expression alters cell destiny and leads to cancer [192]. Dynamic chromatin re-modelling causes aberrant gene expression through enhancer hijacking, as seen in T cell acute lymphoblastic leukemia (ALL) [170]. Experiments have shown that N6 Methylation of Adenosine causes overexpression of *METTL5* gene in numerous human malignancies. In the instance of breast cancer, *METTL5* gene overexpression promotes carcinogenesis and hinders the translation process [186]. In mouse models, *METTL5* overexpression causes tumor growth, whereas in *C. elegans*, enhanced METTL5 enhances thermotolerance, life span, and the unfolded protein response pathway [72].

Structural diversity in G-quadraplexes causes variance in p53 levels, which promotes tumor growth. However, recent research has shown that the splicing regulatory factor SRSF1 interacts with G-quadruplexes [127], FTO overexpression and lower METTL3 mRNA levels have been seen in lung metastasis [186]. Human malignancies such as acute myeloid leukemia (AML), breast cancer, and glioblastoma multiforme (GM) exhibit heterogeneity in 2'-O methylation and abnormal rRNA alteration [56].

Modification of 2'-O M sites activates oncogenes and promotes cancer. In lung cancer, the *SNORD88C* gene is activated to induce translation of the stearoyl COA desaturase 1 enzyme, which inhibits autophagy and promotes tumor growth and metastasis [197]. Abnormal deposition of pseudo uridine Ψ can alter p53 translation, resulting in DNA damage and cancer susceptibility in patients [15]. Changes in small nucleolar RNA (snoRNA) expression cause the alteration of two pseudo uridines at U609 and U863, resulting in oncogenic activation. Furthermore, snoRNA overexpression and pseudo uridylation produce high grade severe ovarian cancer in humans [112]. Consequently, m5C, m6A, and m'acp3Ψ rRNA base changes have proved to be crucial for ribosomal functioning. Dysregulation of these leads to variable tumor development in the person [112].

Aberrations in miRNA biogenesis have been linked to a variety of human illnesses. Mutations in DROSHA, DGCR8, and DICER1 have been linked to cancer [50], as well as AGO in neurodevelopmental disorders [189]. miRNA affect the signaling network by either upregulating or downregulating signals. miR-885-3P, miR208b, and miR-181c are used to regulate the phosphoprotein network [50]. After synthesis, pri-miRNAs form a hairpin loop exposes the base of the nuclear microprocessor complex [89]. These complexes contain the RNA polymerase III enzyme DROSHA and DGCR, which work together to cleave every hairpin and produce a single hairpin of pri-miRNA (55-70 nucleotides long). Transcribed pri-miRNA shortens within the nucleus and undergoes changes such as base exchange and phosphorylation [50]. DICER1 syndrome has been documented in cases of hereditary pleuropulmonary blastoma in children [118]. Somatic missense mutations in DROSHA affect miRNA processing, resulting in Wilm's genitourinary tract tumor [43]. A single amino acid mutation in AGO2 causes neurological illnesses in people with intellectual disabilities, resulting in RISC formation.

miRNA is found in the 3'UTR region of mRNA, controlling active expression and forming a complex network. As a result, miRNA sequesters connections between RNA binding proteins and mRNA that regulate gene expression when these two recognize the same sequence and modify activity [121]. In cardiomyocytes, target mRNAs are inhibited due to miR34a modifications. Upregulation of METTL3 and METTL14 has been discovered in individuals with coronary heart disease [31]. Adenosine deaminase (ADAR) is thought to be involved in smooth muscle contractions by editing RNA from adenosine to inosine. Patients with cardiovascular illnesses have ADAR overexpression, which leads to RNA alteration and causes vascular inflammation, angiogenesis, and cell death [128].

In bacteria and many diseases, the 5' UTR of mRNA has a structural pattern known as riboswitches [7]. Riboswitches control gene expression 'ON' and 'OFF' by changing conformation to inhibit transcription and sequestering the ribosome binding site during translation initiation. The proximity of RNAP influences the folding of the riboswitch, affecting transcription and translation in bacteria [48]. *Bacillus subtilis*, a gram-positive bacterium, has four highly conserved guanine riboswitches: xpt-pbux, pbu-G, nup-G, and pur. The attachment of guanine riboswitches causes suppression of downstream genes. However, antibiotics can lower the chance of escape in clinical settings by regulating gene expression via the riboswitch and protein interface [48]. Further research has demonstrated that cellular and viral mRNA secondary structures contain cis regions in the 3' UTR that promote mRNA stability.

Globally, it is argued that viral mRNA is transcribed from overlapping strands, resulting in the formation of dsRNA in DNA virus infected cells [132]. The IRES (internal ribosomal entry site) in viral translation at the 5' UTR is complex in structure and recruits translational machinery into host cells, boosting its pathogenicity in SARS-COV-2virus [167]. Other RNA viruses, such as Ebola, Zika, and Influenza, have compact genetic material that can interweave with the host's RNA structure, dramatically affecting viral infectivity and pathogenicity in host cells [167]. Thus, viruses use planned RNA transitions to continue through their life cycle in the host. RNA thermometers govern virulence factor expression; for example, in leishmania, melting of the 3'UTR promotes translation, resulting in infections [83].

6.RNA therapeutic applications

RNA regulates both health and disease processes in all living creatures. The three-dimensional structure allows it to perform these vital activities. In recent years, there has been an increased interest in using small compounds to target organized areas of RNA. This technique provides essential chemical tools for understanding fundamental biological processes, as well as the potential to produce new medicines to cure diseases for which there are now no viable treatments. Recent years there has been a surge in research and public interest in RNA-based therapeutics [114]. RNA can take various forms, including mRNA, siRNA, miRNA, ribozymes, and non-coding RNAs, depending on its function [119]. RNA is currently used for gene therapy [98]. Furthermore, RNA is used as a building block to create RNA nanostructures. Despite the obstacles of employing RNA for therapy due to its natural inclination to degrade, advancements in RNA nanotechnology have resulted in more stable RNA structures, making them more effective. Various approaches have been developed to improve the durability of RNA nanostructures, allowing them to be employed within the body [191]. Each RNA fragment contains a distinct component that can act as a receptor-binding molecule, an aptamer, a short interfering RNA, or a ribozyme [37]. RNA aptamers can build complex structures and bind strongly and selectively to many big molecules, viruses, and cells [54] and [169].

The first aptamer-based therapy was approved by the FDA in 2005, and several new aptamer-based treatments are currently being tested in clinical trials to treat conditions such as macular degeneration, intravascular thrombus, acute coronary syndrome, von Willebrand factor disorders, angiomas, AML, non-small cell lung cancer, and a variety of other diseases [169]. Since the last two decades, antisense oligonucleotides (ASOs) have been known for their capacity to influence RNA processing and control protein creation. In recent years, this constant improvement has reached a notable high with the approval of ASOs for treating Spinomuscular atrophy (SMA) and Duchenne muscular dystrophy (DMD),, marking significant milestones in a field where disease-modifying medicines were nearly non-existent [149]. Since the previous decade, miRNA and siRNA have been the most extensively investigated RNA molecules [84]. This is reflected in nearly 20 clinical trials to test their efficacy as therapeutics, including TargomiR (miR-16 mimic-based therapy) in mesothelioma, Cobomarsen (anti-miR-155) in T-cell leukemia/lymphoma, and Miravirsen (anti-miR-122) in hepatitis C patients [95], [122] and [5].

MicroRNAs (miRNAs) are little RNA molecules that do not contain genetic instructions. They typically function by blocking the process of producing proteins from messenger RNAs, which are responsible for carrying genetic information [124].

This aids in the regulation of genes involved in a variety of cell functions, including development, homeostasis, and cell death. When their activity is interrupted, cancer may spread [42]. MiR-34 has the potential to become a new therapy option for numerous types of cancer due to its broad range of activity [12]. Experimental evidence indicates that rectifying specific miRNA modifications with miRNA mimics or antagomirs can restore normal function to the gene regulatory network and signaling pathways, as well as transform the features of malignant cells back to normal [137]. MiRNA-based gene therapy offers a promising anti-tumor strategy for integrated cancer treatment [64].

Small interfering RNA (siRNA) is a type of non-coding RNA that influences and controls gene, RNA, and protein function [134]. Several siRNA-based therapeutics have been developed to treat various diseases, including cancer, viral infections, and genetic disorders [10] and [126]. RNA vaccines based on messenger RNA or self-amplifying RNA replicons could overcome the limitations of plasmid DNA and viral vector-based vaccines [175]. Mockey [125] studied a method for inhibiting the progression of melanoma in mice models by utilizing mRNA that encodes the melanoma-associated antigen known as MART1. This procedure entailed injecting the mRNA into the cytoplasm of dendritic cells in a laboratory setting containing CD8+ cytotoxic T lymphocytes, which, when activated, can destroy tumor cells. Chemical small molecules targeting RNA stability influence the longevity of certain RNA molecules by either protecting them from degradation or hastening their demise. Compounds can bind to and lock down certain RNA secondary or tertiary structures (such as bulges and loops). RNA structure broadens the "druggable" genome, enabling interventions against transcripts and genes that were previously thought hard to target with traditional protein-inhibiting medicines [161]. Targeting RNA-binding proteins with small compounds is a growing area of drug discovery research. Bifunctional compounds stand out as particularly intriguing since they offer potential solutions to several of the common issues encountered when developing therapeutics targeting RBPs [106].

The advantages and disadvantages currently employed methods are discussed in the next paragraph. Unlike typical protein targets, RNA has a highly charged, dynamic, and diverse structure environment, making it a promising frontier in drug development [32]. mRNA is preferred over other methods of gene editing for a variety of reasons. First, it provides rapid, ubiquitous, and transitory protein production, making it easier and safer to give. Furthermore, modified mRNA avoids the issue of inducing an early immunological response before the antigen is delivered to cytotoxic T cells, which can happen with protein or subunit-based delivery techniques [82]. The laboratory results, however, revealed that mRNA is extremely unstable within the body and is easily damaged by immunological agents and nucleases. It also has the potential to elicit detrimental immunological responses [96]. Furthermore, there are numerous hurdles to employing these RNA-targeted small compounds in clinical applications [186]. Experimentally introducing RNA into cells can affect the function of an endogenous gene in certain natural systems due to the antisense mechanism. Because RNA is versatile, non-specific preventing off-target toxicity are the main challenges in medicinal chemistry. Advanced systems explore the transcriptome for accessible RNA motifs, increasing the feasibility of targeted ligand design [81].

Developing effective medicines for use inside the body is dependent on a number of essential elements, including stability and delivery. Nanoparticles, such as lipids and polymers, are frequently employed to transport these treatments because they are small enough to easily reach and distribute to cells [191] and [190]. RNA nanoparticles are utilized to treat cancer and viral infections, but their instability has limited their therapeutic applications. The absence of strong chemical connections or crosslinks in these nanoparticles causes them to break down in the body. It has been established that the packing RNA from the bacteriophage phi29 DNA packaging motor may be generated from 3 to 6 RNA fragments without the use of metal salts.

7. Discussion

Aside from its role as a transporter of genetic information, cellular RNA participates in a variety of important regulatory functions. Three-dimensional structures of RNA, either alone or in association with proteins, are critical for understanding the molecular mechanisms of RNA function. RNA's minimal chemical complexity allows it to adopt flexible forms that alter depending on the environment and binding partners. Changes in RNA structure frequently function as a molecular switch, changing RNA conformations in response to biological inputs. This shape-shifting capacity, seen in both non-coding and messenger RNAs, affects essential processes such as gene expression [184], splicing [110], and translation [40] without affecting the underlying genetic code. These important processes are controlled by RNA elements. Multiple copies of cis elements with additive functional effects, as well as a constellation of trans-binding partners (such as proteins, microRNAs, or other RNAs), strengthen these regulatory clusters against mutation-induced perturbations and allow fine-tuning of the concerted output. RNA conformation is a very dynamic process, with eukaryotic 5' UTRs routinely adopting different conformations in dynamic equilibrium [105]. Depending on the cellular environment, mRNA can switch between a structured, inaccessible state (which inhibits translation) and a relaxed, single-stranded state [59]. Each of these biophysical events necessitates multiple components in order to initiate and complete the process without errors and in various cellular conditions. Reductionist biochemical work on model systems revealed that the same RBPs can control translation through several mechanisms, which are frequently influenced by other RBPs in a combinatorial manner. Current advancements in the field include modeling of RNA tertiary structures, which is critical for understanding their roles in complex biological machinery and, eventually, aiding their design for molecular computing and robotics. In recent years, a concerted effort to improve computational prediction of RNA structure has expedited progress in the field. Current molecular modeling software can simulate RNAs in the 100-300 nucleotide size range with continuous subhelical precision (~ 1 nm) [27]. Pairing and stacking of bases is the most visible and energetically crucial characteristic of RNA structure. Almost all bases in long RNAs or RNPs are stacked and paired, however the stacking can be with intercalated small molecules or protein aromatic side chains, and the pairing is not always canonical Watson-Crick [195]. Base pairs can diverge significantly from co-planarity while maintaining strong H-bonding. RNA-binding proteins identify these structures by particular intermolecular hydrogen bonding, salt bridges, and (pi)-stacking interactions [33].

The complexes frequently enrich certain amino acids such as lysine, tyrosine, and glutamine to interact with the uneven geometry.

It is expected that reductionist mechanistic investigations using biochemical approaches and transcriptome-wide, time-resolved *in vivo* analyses, including ribosome profiling, will combine to provide unprecedented insights into translation and translational control, both at the individual mRNA and transcriptome levels. Table-2. Provides a summary of cis RNA detection methods. Among eukaryotes, regulatory RNA pathways are clearly conserved between animals and plants. However, the literature contains considerable gaps regarding the molecular processes of the suggested interactions between eukaryotes and bacteria. Careful comparisons of the molecular mechanisms of RNA-mediated gene regulation in eukaryotes and bacteria should greatly benefit progress in the field of inter-domain communication [102].

Because EVs and regulatory RNAs are produced directly or indirectly by all forms of life, RNA encapsulated in EVs could facilitate communication across all organisms, including distantly related eukaryotes and bacteria. Thus, this RNA region could promote inter-kingdom biology. Another avenue of genome regulation, known as chromatin-associated RNAs (caRNAs), has recently been postulated. Examples include the long non-coding RNAs Xist and Neat1. Chromatin-associated RNAs can directly affect histone packing by base-pairing with genomic DNA; however, through a more typical approach, RBPs that bind to a specific sequence or alteration of caRNA can recruit several nuclear proteins that change the local chromatin state. RBPs may bind and stabilize these nascent transcript RNAs, or they could anneal back to their template DNA, forming an R-loop structure.

Table 2: Methods of cisRNA detection

mRNP detection methodology	Protocol	Application/Reference Gebauer et al., 2012
Photoactivatable-ribonucleoside-enhanced cross-linking and immunoprecipitation (PAR-CLIP).	Cultured Cells with containing 4-thiouridine (4SU), leading to incorporation of the photoactivatable nucleoside. Cross-linking with UV light of 365 , immunoprecipitation, and purification by denaturing gel electrophoresis. Isolated RNA fragments are identified by nextgeneration sequencing.	Identifying exactly which RNAs interact with specific proteins to regulate **splicing, stability, and translation**
GRNA chromatography	A fusion of lN peptide with glutathione S-transferase (GST), and incorporation of the boxB hairpin into bait RNA converts glutathione Sepharose into an RNA affinity matrix (GRNA resin), which is incubated with cellular extracts. Proteins specifically bound to the matrix are eluted and identified by mass spectrometry.	Separate, purify, and characterize the single-guide RNAs (sgRNAs)
Interactome capture	RNP crosslinking in living or as in the PAR-CLIP approach. (m)RNPs is purified by binding to an oligo(dT) Specifically bound proteins are released by RNase digestion and identified by mass spectrometry	Discover the complete repertoire of **RNA-binding proteins (RBPs).** how these interactions dynamically change in response to physiological cues, stress, or diseases
Mapping RNA interactome in vivo (MARIO)	RNA molecules and their co-bound proteins are cross-linked together within living cells. Target RNAs are attached to a custom, biotinylated RNA linker. The resulting chimeric RNAs (in the configuration of RNA_1--Linker--RNA_2) are isolated using magnetic beads and subjected to paired-end sequencing.	High-throughput sequencing technology developed to capture pairwise RNA-RNA and RNA structure interactions directly inside unperturbed living cells
Cross-linking ligation and sequencing of hybrids (CLASH)	Living cells are exposed to UV light, The target protein (the "bait") is carefully purified to isolate only the complexes it is associated with The interacting RNAs (for example, a miRNA and its target mRNA) that are held together within the protein complex are ligated (joined) to form a single continuous RNA molecule The ligated "chimeric" RNAs are reverse-transcribed into cDNA, sequenced, and analyzed using bioinformatics pipelines to reveal exact interaction sites.	An advanced molecular biology technique used to map direct, physical RNA-RNA interactions in living cells. It is primarily used to identify specific targets of microRNAs (miRNAs) and other RNA-binding proteins (RBPs).
SAXS	X-rays are scattered by the RNA and surrounding ions in solution. Algorithms like DENSS or MONSA can convert these profiles directly into three-dimensional molecular shapes. Anomalous scattering (ASAXS), can be used to map the spatial distribution of these counterion clouds.	Low resolution Captures full conformational space as average Flexible with respect to size

The manipulation of RNA *cis*- and *trans*-acting elements has emerged as a powerful strategy for improving plant biotechnology and engineering. By modifying existing regulatory elements or introducing novel ones, researchers can alter gene expression patterns, enhance desirable agronomic traits, and improve the production of heterologous proteins in plants. The regulatory activity of these elements is determined not only by their nucleotide sequences but also by their dynamic secondary and tertiary structures, which influence interactions with RNA-binding proteins, ribosomes, and other regulatory factors. RNA structural elements located within the 5′ untranslated region (5′ UTR) play particularly important roles in the regulation of translation initiation. Strong secondary structures within the 5′ UTR generally reduce translation efficiency by limiting access of the pre-initiation complex (PIC) to the mRNA. For example, stable stem-loop structures or G-quadruplexes positioned near the 5′ end can hinder ribosome recruitment and impede translation initiation.

During ribosomal scanning, RNA helicases such as eukaryotic initiation factor 4A (eIF4A) facilitate the unwinding of secondary structures. However, highly stable stem-loops and G-quadruplexes can resist unwinding, thereby reducing translational efficiency. Such regulatory mechanisms have been extensively demonstrated in plant systems and represent important targets for translational engineering.

Beyond their inhibitory effects, RNA structural elements can also mediate conditional and environmentally responsive translational regulation. A notable example occurs in vascular plants, where translation of the SUPPRESSOR OF MAX2-LIKE proteins SMXL4 and SMXL5, key regulators of phloem differentiation, is controlled through the formation of a G-quadruplex structure within the 5′ UTR. This process is facilitated by the sucrose-inducible RNA-binding protein JULGI, providing a mechanism by which metabolic signals can directly influence developmental processes through RNA structure-dependent regulation.

Riboswitches represent another class of RNA regulatory elements with considerable biotechnological potential. Thiamine pyrophosphate (TPP) riboswitches have been successfully utilized to regulate gene expression in both *Arabidopsis thaliana* and tomato seedlings, demonstrating the feasibility of employing metabolite-responsive RNA elements for precise control of transgene expression. Such systems offer valuable tools for the development of inducible gene expression platforms in plants. In addition to endogenous gene regulation, *trans*-acting catalytic RNAs have been exploited to enhance plant resistance against pathogens. Engineered ribozymes targeting viral and viroidal RNAs have been introduced into transgenic plants, resulting in reduced pathogen accumulation and decreased symptom severity. These approaches illustrate the potential of RNA-based technologies for developing disease-resistant crop varieties without directly altering the host genome, plastids provide an attractive platform for metabolic engineering owing to the remarkable diversity of biochemical pathways they harbor. Manipulation of RNA regulatory elements within plastid genomes can facilitate the enhanced biosynthesis of valuable endogenous metabolites, including carotenoids, vitamins, and antioxidants. Moreover, plastids can be engineered to express heterologous enzymes that utilize plastid-derived substrates for the production of novel compounds, such as biodegradable bioplastics and industrially relevant metabolites. Consequently, the integration of RNA-based regulatory strategies with plastid engineering offers significant opportunities for improving crop productivity, nutritional quality, pharmaceutical protein production, and sustainable biomanufacturing.

Overall, advances in the understanding of RNA *cis*- and *trans*-acting elements are providing new avenues for precise control of gene expression in plants. The ability to engineer RNA structure and function has the potential to transform plant biotechnology by enabling the development of crops with enhanced productivity, stress tolerance, disease resistance, and metabolic capabilities.

Conclusion

Reductionist biochemical research on model systems has shown that the same RBPs can affect translation through several mechanisms, frequently in a combinatorial manner with other RBPs. After decades of mapping cis-acting elements and identifying trans-acting factors primarily by biochemical and genetic methods, the study of mRNA translation has now moved into a phase of transcriptome-wide, highly parallel investigations. These methods have started to provide a picture of dense mRNP assemblies containing numerous trans-acting factors and assist in identifying RBP-binding sites throughout the transcriptome.

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Dedications to the Lotus feet of Bhagavan and the gurus of Sringeri Peetam

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