Coregulatory mechanism and interactome network of miRNA, lncRNA, and mRNA involved in human diseases

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INTRODUCTION

The protein-coding genes have been extensively investigated and are considered the most thoroughly examined components of the genome and transcriptome. However, it is essential to note that they constitute less than 2% of the genome. Merely comprehending the roles and activities of messenger RNAs (mRNAs) is insufficient to provide a comprehensive picture of the cellular machinery. To have a more thorough understanding of the intricate control of biological processes, it is imperative to investigate the substantial portion of the genome and transcriptome that remains unexplored and understudied. These constituents are responsible for the modulation of gene expression. Noncoding RNAs (ncRNAs) represent a significant constituent inside biological systems. They are categorized into many classes based on their dimensions, configurations, and purposes. RNAs can carry out a variety of tasks, including catalyzing enzymatic activities (e.g., ribozymes), regulating protein synthesis (e.g., miRNAs), increasing protein production [e.g., long noncoding RNA (lncRNAs)], altering the protein that is produced by an mRNA (e.g., riboswitches), and many more [1]. Vast amounts of data are now easily accessible thanks
to the development of contemporary sequencing technologies and the accompanying drop in sequencing cost [2]. This enables us to have a comprehensive understanding of the functioning of the cellular machinery and the emergence of disease, which in turn pave the way to finding a cure for these diseases.

Loss of balance in these relationships can lead to many disorders, including cancers, cardiovascular disorders, and neurological diseases [3,4]. This review discusses several of these disorders and the RNAs involved in them. These relationships can potentially be utilized as therapeutic targets to help combat these illnesses [3]. Ever-increasing rates of cancer, cardiovascular diseases, and relatively weakly addressed neurological disorders are the prime focus of this review. This review not only highlights the different RNA and their roles, but also brings to the attention of the scientific community the interplay between them and their further cascading implications. This kind of cohesive, comprehensive, and informative documentation of RNA involving the aforementioned diseases is not available thus far, and therefore, it will significantly help scientists in the future to identify markers [5].

ROLES OF miRNA, IncRNA, and mRNA IN GENE EXPRESSION AND THEIR BIOGENESIS

Role in gene expression

Regulation of gene expression has a much more significant impact on organism complexity than gene count or genome size. The control of gene expression plays a critical role in determining a cell’s identity [6], functions [7], interactions [8], and ultimately, its fate [9].

Different facets of gene expression are regulated by interactions among mRNA, lncRNAs, and miRNAs. mRNAs directly affect the proteome [10], the physicochemical characteristics of the cell, and the protein-coding process. The miRNAs act to quiet the target mRNA and stop it from being translated into proteins [11]. They can accomplish this by either signaling for the target mRNA's destruction or by impeding its translation [12]. This is influenced by the miRNA's target (often the 3′ untranslated region (UTR) of mRNA) and how similar their sequences are.

On the other hand, lncRNAs bind to miRNAs, preventing them from either starting gene transcription or silencing mRNAs, both of which result in the expression of proteins [13]. Figure 2 provides a general understanding of these connections.

MicroRNAs prevent mRNA translation. As a result, miRNA target proteins are downregulated. mRNA’s 3′ UTR (UTR) is where miRNAs find their targets. The miRNA-RISC complex breaks down the mRNA if the target is complementary. The complex prevents the translation of the mRNA if the sequence complementarity is lower [14].

Biogenesis of miRNA, IncRNA, and mRNA

A basic overview is given in Figure 1 below.

Biogenesis of miRNA

miRNA can be produced from specific miRNA genes (in the intergenic area) or as an intragenic component of other gene transcripts (known as mirtrons) [12], employing either their own promoters or those of the host gene [15]. RNA Polymerase II transcribes them to create pri-miRNA, which folds into a stem-loop structure. The expression of miRNAs can be upregulated or downregulated because of a positive or negative feedback loop during transcription [16].

Endonuclease Drosha RNase III and the dsRNA binding protein DGCR8 (DiGeorge syndrome critical region gene 8), also referred to as Pasha [12], cleave the transcribed pri-miRNA in the nucleus. The 5′ phosphate is left unharmed when it cleaves both strands of the hairpin structure, leaving a roughly 2-nucleotide overhang at the 3′ end [17]. The resulting structure is known as pre-miRNA. Instead of using this mechanism, mirtrons go through splicing to create the pre-miRNA [18]. With the aid of Exportin-5 and Ran-GTP, the pre-miRNA is then exported from the nucleus to the cytoplasm [19].

In the cytoplasm, the endonuclease Dicer [20] recognizes the 3′ overhang and 5′ phosphate and cuts the pre-miRNA. Dicer contains a helicase, dsRNA binding domain, a PAZ domain, and two RNase III domains. When the pre-miRNA is loaded into the Dicer, the loop in pre-miRNA is recognized by the helicase domain, while the strands are cleaved by the two RNaseIII domains. This separates the loop and leaves a ds-miRNA:miRNA* complex [21]. One of these strands is the actual miRNA, whereas the other strand, the “miRNA*” is a short-lived, opposing arm of the actual miRNA.

The RISC has been loaded with the miRNA-miRNA* combination (RNA-induced silencing complex). Agronaute-2 protein, Dicer, siRNAs, ADAR1, TRBP, PARN, RNA helicase, Hsp90, TSN, and eIF1A are all components of RISC. Pre-mRNA uptake and the release of Dicer are both affected by Ago-2. To cleave the pre-3′ miRNA’s arm before Dicer processes it, it also has endonuclease activity [22]. Dicer cuts the miRNA* strand, and a loaded RISC complex is now available. Following this, Ago-2 leads the complex to the target mRNA, which is identified by a conserved region of the miRNA [23]. If the miRNA is highly complementary to the target mRNA, the target mRNA is either cleaved or the translation of the mRNA is suppressed [14].

Biogenesis of IncRNA

Depending on the IncRNA itself, the type of cell, and its stage, different IncRNA biogenesis pathways exist. The DNA can contain intergenic regions (lincRNAs), promoter upstream transcripts (PROMPTs), antisense regions (NATs), and enhancers, among other places where they can be translated (eRNAs). Some IncRNA biogenesis resembles that of mRNAs in many ways. There are specific IncRNA genes, and RNA polymerase II is responsible for their transcription. They are produced in regions with chromatin states that are comparable to those of mRNAs [24]. They also go through 3′ poly-A tail, 5′ end m7G capping, and splicing.

However, a number of additional IncRNAs go through unusual processing. Some are subjected to RNase-P maturation [25], others are capping at the 5′ end [26], some are capping both the 3′ and 5′ ends [27], or they may fold into circular structures that stop their degradation [28]. After their biogenesis, they can either be transferred to the cytoplasm...
or enriched within the nucleus itself [29]. The NXF1 (nuclear RNA export factor-1) pathway is used for the transport. They interact with different RNA-binding proteins in the cytoplasm, which helps them get to their target organelles [30].

**Biogenesis of mRNA**

The TATA box region of the gene promoter, which is situated around 25 nucleotides upstream from the transcription start point, is where transcription factor TFIID attaches to begin transcription. TBP oversees identifying the area (TATA-binding protein). The DNA strands become separated as a result. By clearing a path for their binding, RNA Polymerase II and TFIIH form a transcription initiation complex. The TFIIH’s DNA helicase begins to unwind the DNA strands. A protein kinase found in TFIIH phosphorylates the RNA polymerase II C-terminal domain (CTD), improving the enzyme’s ability to bind to the gene and begin transcription. During RNA transcript elongation, the transcription factors are eliminated [31].

RNA alterations take place concurrently with transcription in eukaryotes [32]. This includes 3’ polyadenylation [33], mRNA splicing [34], and 5’ end m’G capping [35]. The mRNA can endure in the cytoplasm thanks to these changes. As the RNA transcript is created from the 5’ end, guanylyl transferase performs the capping process first. Following the transcription and subsequent removal of the introns is splicing by spliceosomes. By using Poly-A polymerase, the 3’ end is polyadenylated last.

**ROLE IN DISEASES**

**Role in cancers**

**Gastric cancer**

With over a million new cases each year, gastric cancer is the most common cancer that results in mortality worldwide. It is the fourth and seventh most diagnosed cancer in men and women, respectively [36]. Numerous genetic variables are also known to play a substantial role in the onset and progression of gastric cancer in addition to the viral causes. These may be inherited or may be dysregulated because of environmental or lifestyle factors [37].

By homophilic interaction with the cytoskeletal elements and plasma membranes of neighboring cells, E-cadherins, calcium-dependent adhesion molecules, help form adherent junctions between those cells [38]. As a result, they are crucial in reducing cell invasion and migration in tumors [39]. Premature stop codons, or PTCs, are inserted by about 80% of all CDH1 germline mutations [40] (premature termination codons). The CDH1 protein is subsequently prematurely terminated as a result. As a result, the CDH1 mRNA in the PTC
is drawn to and degraded by the NMD machinery, severely inhibiting the expression of E-cadherin (Table 1).

The microRNA miR-29b/c is reported to function as a suppressor of tumor metastasis in gastric cancers. It acts by targeting the DNMT3A gene, which codes for DNA Methyltransferase 3 Alpha, which is involved in the methylation of cytosine in the DNA. miR-29b/c is complementary to the 3′ UTR of the DNMT3A mRNA, hence involved in its downregulation. On the other hand, DNMT3A also suppressed miR-29b/c by methylating its promoter. This forms a negatively regulating feedback loop between the two [41]. DNMT3A is involved in promoting gastric tumor cell migration. Knockdown of DNMT3A also leads to an overexpression of the CDH1 gene, thus promoting cell tumor migration.

miR-29b/c is also involved in the regulation of the CDH1 gene. It was reported that miR-29b/c prevents promoter methylation of the CDH1 gene, leading to suppression of its downregulation [42]. Higher expression of CDH1 leads to a lower ability of the tumor cells to migrate. Another gene playing a notable role in gastric cancer is the PCDH10 gene, which codes for Protocadherin-10. Protocadherins are the largest subgroup within the cadherin superfamily. In addition, they aid in the prevention of stomach cancer. In addition, it has been stated that PCDH10 mediates the tumor-suppressive effects of p53. Substantial upregulation of the lncRNA HOTAIR has been observed in gastric tumors. It functions by lowering PCDH10 gene expression by increasing methylation of the PCDH10 promoter [43]. In addition, both the transcriptional and translational levels of p53’s expression are considerably decreased by HOTAIR [44]. The connection between HOTAIR, miR-148b, and DNMT1 controls the methylation process. HOTAIR behaves
as a competitive endogenous RNA (ceRNA) because it serves as a miRNA sponge for miR-148 [45].

In addition, MALAT1 suppresses the expression of the PCDH10 gene to encourage cell invasion and migration in gastric cancer [46]. This is accomplished by the Polycomb Repressive Complex 2 (PRC2), whose active member, EZH2 (Enhancer of Zeste Homolog 2) [47], catalyzes the trimethylation of histone 3 Lys27 (H3K27me3) [48]. MALAT1 also interacts with EZH2 to partially repress CDH1 in gastric cancers [49], but not in renal cell carcinoma cell lines [50].

**Lung cancer**

Lung malignancies are to blame for over half of all cancer-related fatalities [51]. The CDH1 gene also has a substantial impact on lung cancer, like in the case of gastric malignancies. As is well known, CDH1 inhibits cancer cell invasion and migration by improving the cell’s adhesion to nearby cells through adherens junctions. A lncRNA NSCLCAT1 was reported to increase cell invasion and migration in nonsmall cell lung cancers (NSCLCs). NSCLC accounts for 85% of all lung cancers. E-cadherins coding the CDH1 gene are the target of the NSCLCAT1 lncRNA, leading to the downregulation of CDH1 [52]. It is reported that in NSCLC tissues, there is an upregulation of lncRNA NSCLCAT1, and mRNAs TAZ and YAP1 [53]. These were related to a downregulation of mRNAs CDH1, Lats1, and Mst1. These genes are a part of the hippo signaling pathway, which is involved in the inhibition of cell proliferation, limiting cell size, and promotion of apoptosis [54].

Numerous malignancies, including lung cancer, have been associated with the upregulation of the Phospholipase D (PLD) gene [55]. PLD is believed to lower apoptosis and boost cell growth. In lung and other malignancies, several miRNAs, including miR-132, miR-27a, miR-122, miR-21, and miR-10b, have been associated with cancer metastasis, cell survival, and cell proliferation [56]. PLD is involved in the hydrolysis of phosphatidylcholine to phosphatidic acid, which is known to be a key up-regulator of the mTOR (mammalian target of rapamycin) signaling pathway [57]. mTOR acts as a regulator for cellular metabolism, proliferation, growth, and survival [58]. PLD inhibition is linked to a 13.6-fold increase in the expression of lncRNA ANRIL. This increased more when the lung tumor cells were exposed to more PLD inhibitors [59]. Higher expression of ANRIL was reported to increase apoptotic cell death in tumor tissues. It also increases the expression of ATG6/BECLIN-1 [60], ATG3 [61] (autophagy-related gene 3), ATG5 [62] (autophagy-related gene 5), and LC3B [63].

A lncRNA known as GAS5 (Growth Arrest Specific 5) is markedly downregulated in NSCLC. In lung malignancies, GAS5 functions as a tumor suppressor. The transcription factor E2F1 (E2F transcription factor 1), which is involved in the progression of the cell cycle, apoptosis, and DNA-damage response [64], is downregulated by GAS5 expression while the expression of the tumor suppressor p53 is upregulated [65]. It has been demonstrated that miR-10b expression and Klf4 (Krüppel-like factor 4) expression are related. Klf4 is a conserved transcription factor with zinc fingers that is involved in cell growth and proliferation [66]. It is one of four transcriptional factors that are employed to create iPSCs [67] (induced pluripotent stem cells). In tumor cells and stem cells, Klf4 is overexpressed. Through an unidentified relationship, higher Klf4 expression is induced by higher miR-10b expression, which increases NSCLC cell invasion and proliferation [68].

**Breast cancer**

When compared to paracancerous tissues (tissues less than 2 cm away from the boundary of the tumor), lncRNA SNHG7 (small nucleolar RNA host gene 7) has been found to be substantially overexpressed in breast cancers [69]. They are known to encourage the growth and spread of the tumor, serving as an oncogene [69]. The stage of the tumor and the spread of the cancer to the lymph nodes and organs were found to be directly linked with the expression of SNHG7. According to research, cancer was found to be more aggressive when SNHG7 expression was higher, which decreased the patient’s chance of survival [70]. It functions by absorbing miR-186 like a sponge. Cell migration and proliferation are known to be inhibited by microRNA-186 [71].

Higher SNHG7 was associated with increased chemoresistance of breast cancer cells to chemotherapeutic agents such as Adriamycin [72] and paclitaxel [73]. In addition, miR-34a is absorbed by SNHG7 [74]. The presence of SNHG7 was observed to negatively correlate with miR-34a expression in chemoresistant cells, indicating that miR-34a is one of lncRNA SNHG7’s targets [75]. MiR-34a is responsible for downregulating Bcl-2 (B-cell Lymphoma 2) and SIRT1 (Sir2 homolog 1), which leads to inhibited proliferation and migration of cancerous cells [76]. Its sequestering by SNHG7, thus, contributes to the disease.

Other than SNHG7, other lncRNA also interact with miR-186 to regulate the development of breast cancer. One such lncRNA is LINC01705 [77]. It also acts by sponging miR-186, leading to the advancement of cancer. Thus, the proliferation and metastasis of cancer are higher in cells with a higher expression of LINC01705. A decrease in the expression of LINC01705 led to an increase in tumor cell apoptosis, though the mechanism is not clear. Localization studies show that the lncRNA is mostly found in the cytoplasm, indicating that it may perform its regulatory roles post-transcriptionally [78].

**Hepatocellular carcinoma**

Liver malignancies express a lot of the lncRNA highly elevated in liver cancer (HULC) [79]. In hepatocellular carcinoma (HCC), it is the lncRNA that is most overexpressed [80]. In addition, it has been suggested that it is elevated in a number of different malignancies, including osteosarcoma [81], gastric cancer [82], and pancreatic cancer [83]. In various cancer types, HULC has a role in promoting cell proliferation, cell survival, colony formation, cell migration, cell invasion, and angiogenesis [84].

The Eukaryotic translation elongation factor epsilon-1 (EEF1E1) is also sometimes referred to as p18 [85]. In malignant tissues, HULC levels and EEF1E1 levels are inversely correlated [86]. It follows that the suppression of the EEF1E1 gene is one way that HULC upregulates cancer. The enzyme Sphingosine Kinase 1 (SK1) is crucial for the development of cancer [87]. It is involved in the regulation
of sphingolipid levels in the cell. The expression of SK1 was found to be correlated positively with the expression of HULC. It leads to higher levels of Sphingosine-1-Phosphate in HCC and upregulates angiogenesis in these tissues.

An important part of the commencement of the metabolism of long-chain fatty acids is played by the enzyme ACSS1 [85,88]. Positive correlations between the cellular levels of HULC and ACSS1 were discovered [89]. The ACSS1 gene is induced as a result of a decrease in the transcription factor PPARA [85,88]. A hallmark of cancer is the buildup of cholesterol and triglycerides within the cell, which is caused by an increase in ACSS1 expression [90].

MiR-9 is silenced by HULC through epigenetic regulation. MiR-9-3p was identified in HCC cell lines as well as in clinical samples, to act as a tumor suppressor. It does that by targeting the expression of the TAZ protein. Inhibition of TAZ protein leads to reduced cell proliferation and reduced phosphorylations of Erk1/2 (Extracellular Signal-Regulated Kinase 1/2), AKT (Serine/Threonine Kinase Family), and β-catenin [91]. This is yet another way in which HULC contributes to the HCC.

Glioma

LncRNA cancer susceptibility candidate 2 (CASC2) is downregulated in numerous malignancies, including glioma [92]. phosphatase and tensin homolog (c), a recognized tumor suppressor, is upregulated by it. In addition, CASC2 directly inhibits miR-181a, which likewise inhibits the Akt signaling pathway [93]. It also contributes to the downregulation of miR-193a-5p expression, which lowers the therapeutic effectiveness of temozolomide [94]. This is accomplished by CASC2 activating the mTOR pathway.

The lncRNA HOTAIR is suggested to be involved in glioma, enhancing cell cycle progression via PRC2 [95]. Knockdown of this lncRNA leads to a decrease in the expression of miR-326, which in turn suppresses fibroblast growth factor-1 (FGF1) expression, and blocks PI3K/AKT and MEK1/2 pathways [96]. This leads to an increase in apoptosis and cell cycle arrest, while reducing cell proliferation, cell migration, and cell invasion.

The gene known as Gasdermin D (GSDMD) [97] is crucial for the process of pyroptosis, which in turn affects tumor formation and therapeutic response [98]. When compared to nontumor brain cells, it is found to be elevated in gliomas [99]. The miRNA has-miR-296-5p is one of the main downregulators. The lncRNAs KCNQ1OT1 and LINC01278 are indicative of the development of the disease and have a favorable correlation with GSDMD. Another lncRNA that downregulates the GSDMD gene is MIIRLET7BH, and the expression of this lncRNA is favorably connected with better clinical results for the patient [100].

Oral squamous cell carcinoma

Oral squamous cell carcinoma (OSCC) is thought to be caused by the lncRNA NORAD (ncRNA Activated by DNA damage). According to reports, it is overexpressed in OSCC. One of the targets of NORAD is miR-577, which has been shown to be downregulated in OSCC [101]. Numerous malignancies, including OSCC, have been reported to have dysregulated expression of the TPM4 (Tropomyosin 4) gene [102]. It has been demonstrated that miR-577 adversely downregulates TPM4 in OSCC. Therefore, NORAD affects the development and maintenance of cancer by miR-577-mediated downregulation of the TPM4 gene [103].

The HLA Complex Group 2 lncRNA HCG22 plays a role in a variety of malignancies, including OSCC [104]. Better patient survival is correlated with higher HCG22 expression [105]. The proliferation, invasion, and migration of OSCC cells are inhibited by HCG22 overexpression. Targeting miR-425-5p [106] achieves this. MiR-455-5p is sponged by HCG22, acting as a ceRNA to reduce its availability in the cell. Malignancies, including OSCC, HCC [107], colorectal cancer [108], and cervical cancer [109], to mention a few, have higher expression of miR-425-5p.

Prostate cancer

Prostate cancer too, is affected by the lncRNA NORAD [110]. While blocking apoptosis, it is known to stimulate cell migration and proliferation [111]. It is thought that NORAD also encourages pancreatic cancer bone metastases. As a ceRNA, NORAD targets miR-541-3p. MiR-541-3p’s decreased availability makes (Pyruvate Kinase M2 (PKM2)’s gene expression more prominent. PKM2 is typically present in embryonic and malignant cells and is strongly associated with carcinogenesis, tissue repair, and regeneration [112].

Extracellular vesicles with PKM2 promote metastasis of pancreatic cancer [113]. This gene also affects the internalization and the release of the extracellular vesicles [114]. This is done by PKM2-mediated phosphorylation of synaptosomal-associated protein 23 (SNAP-23), and the formation of soluble N-Ethylmaleimide-sensitive fusion actor attachment protein receptor (SNARE) complex [115]. This leads to the promotion of extracellular vesicle release [116]. These vesicles also contained more ATP, making them easier to be internalized by bone marrow stromal cells [117], which leads to a significant increase in bone metastasis of prostate cancer.

LncRNA that is downregulated in prostate cancer is a Disintegrin and Metalloproteinase with Thrombospondin Motifs 9-9-Antisense 1 (ADAMTS9-AS1). Apoptosis is known to be influenced by the lncRNA. MiR-142-5p expression and ADAMTS9-AS1 regulation are adversely correlated. It is known that this miRNA affects the Cyclin D1 (CCND1) gene. Several tumor suppressors are activated because of CCND1. As a result, increased CCND1 suppression by miR-142-5p [118] and low expression of ADAMTS9-AS promote prostate cancer.

Role in cardiovascular diseases

Acute ischemic stroke

Blood flow to the brain is reported to abruptly halt during an acute ischemic stroke (AIS) [119,120]. As a result, the brain receives significantly less oxygen and glucose. It is increasingly prevalent among middle-aged and older individuals around the world as well as among aging populations. A lncRNA called potassium voltage-gated channel subfamily Q Member 1 Opposite Strand 1 (KCNQ1OT1) has been linked to atherosclerosis and heart attacks, both are major risk factors
Table 2. mRNAs, miRNAs, and IncRNAs involved in cardiovascular diseases.

<table>
<thead>
<tr>
<th>Cardiovascular Disease</th>
<th>mRNA regulation</th>
<th>miRNA regulation</th>
<th>IncRNA regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ischemic stroke</td>
<td>ATG7 (down), LC2B II (down), C1QTNF6 (up)</td>
<td>miR-200a (down), miR-29b (down), miR-210 (up)</td>
<td>KCNQ1OT1 (up), H19 (up), TET2 (down)</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>MAP3K10 (up), COX20 (up), CD79A (up), CEACAM8 (up), CCR7 (up), SPP1 (up)</td>
<td>miR-126 (down), miR-214-5p (down), miR-335-5p (down), miR-371a-5p (down)</td>
<td>TUG1 (up), DANCER (up), COLCA1 (up)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>ABC transporter A1 (up), Sp3 (up), Twf1 (down), SPP1 (up)</td>
<td>miR-223 (up), miR-1 (up), miR-371a-5p (down)</td>
<td>COLCA1 (up)</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>TULP3 (up), Bax (up), Caspase-3 (up), Bcl-2 (down), STAT3 (up)</td>
<td>miR-4688 (down), miR-106-5p (down)</td>
<td>NEAT1 (up), SNHG16 (up)</td>
</tr>
</tbody>
</table>

for stroke [121]. In the plasma of AIS patients, KCNQ1OT1 expression was said to be greater. This lncRNA’s expression is inversely linked with stroke severity [122]. It was discovered that KCNQ1OT1 silencing in mice resulted in a noticeably smaller volume of cerebral infarction [123]. This could be a possible avenue for treatment.

The expression of miR-200a and the expression of the LncRNA KCNQ1OT1 are (Table 2) negatively correlated. Each of them has a negative feedback mechanism that reduces the other’s expression. MiR-200a expression rose when KCNQ1OT1 was knocked down, which increased cell survival and decreased autophagy [124]. This outcome was consistent with the reported decline in the levels of the stress-induced autophagy-related proteins ATG7 [125] and LC3B II [126].

According to reports, ischemic stroke patients’ brains, neutrophils, and plasma had higher levels of the lncRNA H19 [127]. It functions for miR-29b as a ceRNA sponge. Through the control of C1q tumor necrosis factor-related Protein 6 (C1QTNF6), miR-29b is known to contribute to an increase in inflammatory response [128]. The gene for C1QTNF6 is the target of this miRNA. The C1QTNF6 gene encourages TNF release, which aggravates inflammation [129]. Therefore, the increased H19 causes miR-29b to be downregulated, which increases the expression of the C1QTNF gene [130].

MiR-210 is a master hypoxamir (miRNAs that are stimulated by hypoxia) [131], which has been shown in human studies to be a blood biomarker for AIS and other cardiovascular diseases and cancers [132]. It has been proven in animal studies to be very overexpressed in the brain after the stroke. Suppression of its action by miR-210-LNA (locked nucleic acid oligonucleotides) leads to reduced inflammation and a neuroprotective effect [133]. Tet Methylcytosine Dioxygenase 2 (TET2) is an important regulator of proinflammatory cytokines [134]. It has been shown in rats that miR-210 binds to the 3’ UTR of TET2 and downregulates its expression, contributing to the disease [135].

Atherosclerosis

In the medium to large-sized arteries, atherosclerosis is a fat-storage disease with an immunoinflammatory response [136]. Plaque, which is comprised of cholesterol, lipids, and other substances, builds up on the artery walls as a result of this condition. Inflammatory cytokines TNF-α and IL-6 were reduced in mice after the administration of miR-126 [137]. This shows that miR-126 plays a role in the atherosclerotic process’ detrimental regulation of the inflammatory response. MAP3K10, a component of the MAPK signaling pathway, has been found to be another miR-126 target [138]. The process of inflammation causes an upregulation of this pathway. Because miR-126 inhibits the pathway, it plays a role in reducing inflammation [139].

The lncRNA Taurine Upregulated Gene 1 (TUG1) is another ncRNAs involved with atherosclerosis. TUG1 has been found to be strongly expressed in those with atherosclerosis. Its involvement in the illness was confirmed by the fact that it was expressed excessively in the aortic plaques [140]. During hypoxic conditions, the lncRNA is increased in vascular smooth muscle cells (VSMCs) [141]. TUG1 was also discovered to be an up-regulator of proliferation and a down-regulator of apoptosis [142], which may quicken plaque development and heighten disease severity.

In atherosclerotic patients, the lncRNA differentiation antagonizing nonprotein coding RNA (DANCER) is markedly overexpressed. For miR-214-5p [143], DANCER functions as a ceRNA sponge. This miRNA inhibits the production of the cytochrome C oxidase assembly protein (COX20) gene by targeting it. According to reports, COX20 may help a cell become more resistant to oxidative damage and apoptosis [144]. DANCER also acts as a sponge for miR-335-5p [145]. MiR-335-5p is known to have an inhibitory effect on plaque formation in atherosclerosis [146]. This miRNA also targets CD79A, Carcinobryonic Antigen-Related cell adhesion molecule 8 (CEACAM8), and chemokine receptor 7 (CCR7) genes, which are linked to play a role in the disease [147].

Human Coronary Artery Endothelial Cells, or HCAECs, can be stimulated to induce an inflammatory response using oxidized low-density lipoprotein (OxLDL) [148]. The resulting transcriptome change causes these cells to proliferate less. The lncRNA colorectal cancer associated 1 (COLCA1), which is overexpressed, is one of the main variations in expression. According to reports, COLCA1 alters cell biology via miR-371a-5p. This miRNA is linked to cancer [149] and inflammatory response [150]. COLCA1 and miR-371a-5p share a ceRNA relationship. miR-371a-5p targets the 3’ UTR of secreted phosphoprotein 1 (SPP1) mRNA. SPP1 gene has been shown to play an important role in atherosclerosis, and coronary heart disease [151]. It is overexpressed in VSMCs which are a part of plaques formed due to atherosclerosis [152]. As a result, COLCA1 increases the expression of the SPP1 gene, which in
**Table 3.** mRNAs, miRNAs, and lncRNAs involved in brain disorders.

<table>
<thead>
<tr>
<th>Brain Disorders</th>
<th>mRNA regulation</th>
<th>miRNA regulation</th>
<th>lncRNA regulation</th>
</tr>
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<tbody>
<tr>
<td>Parkinson’s disease</td>
<td>NLRP3 (up), TNF-α (up), COX-2 (up), IL-18 (up), IL-6 (up), IL-1 (up)</td>
<td>miR-7 (up)</td>
<td>SNHG1 (up)</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>apoE (up), Apo40 (up), Apo42 (up), GABAB2 (down), BDNF (down)</td>
<td>miR-206 (up)</td>
<td>17A (up)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>BDNF, VEGFA, FGF2, FOS, CD44, SOX2, NRAS, SPARC, ZFP36, FGG, ELAVL1, STARD13</td>
<td>miR-137 (up)</td>
<td>DLX6-AS1, NEAT1, MIRCN, LINC01094, DILAP1-AS1, BABAM2-AS1, PAX8-AS1, ZFHX4-AS1, XIST, MALAT1</td>
</tr>
</tbody>
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Coronary artery disease

A buildup of cholesterol deposits (plaques) in the coronary arteries, which carry blood to the heart, is known as coronary artery disease (CAD). Over time, this build-up causes arteries to constrict, reducing the amount of oxygen that can reach the heart muscles [154]. The coronary arteries’ atherosclerosis is to blame for it.

MiR-223 was identified to be upregulated in patients with CAD, which is also a marker for atherosclerosis [155]. MiR-223 is implicated in the regulation of several genes responsible for inflammation [156]. It also plays a role in the homeostasis of high-density lipoprotein-cholesterol (HDL-C) by inhibiting cholesterol synthesis. MiR-223 indirectly promotes the expression of ATP-binding cassettes (ABC) transporter A1 via Sp3, leading to an increase in cholesterol efflux from the cell [157]. This leads to higher deposits in the coronary arteries, contributing to the disease.

MiR-1 is very highly expressed in the heart but is found to be downregulated in patients suffering from cardiovascular diseases [158] including CAD. It is reported to target Twf1 (Twinfilin) gene [158]. Twf1 is a cytoskeletal regulatory protein that binds to actin monomers to stop actin from assembling. Aortic constriction and other stimuli like α-adrenergic stimulation can cause miR-1 to be downregulated, which causes a high enough level of Twf1 protein overexpression to cause cardiac hypertrophy, a factor in the development of CAD [159].

Several hypoxamiRs are known to play a role in CAD too. One of the important hypoxamiR is miR-146b. Expression of tumor necrosis factor receptor associated factor 6 (TRAF6) is induced in hypoxic conditions in rat cardiomyocytes. The 3’ UTR region of TRAF6 gets bound by miR-146b, leading to a higher expression of IL-6 and CCL2 monocyte chemoattractant protein 1 (MCP-1) [160]. This miR-146b-TRAF6-IL-6/MCP-1 axis plays a role in cardiac dysfunction and failure.

Aortic aneurysm

Aortic aneurysms are bulges in the aorta’s wall [157]. Thoracic aortic aneurysms [161] (TAA) are termed if they develop in the portion of the aorta that passes through the chest cavity, while abdominal aortic aneurysms (AAA) [162] are called if they develop in the portion of the aorta that passes through the belly. The bulge may be saccular [163] (spherical) or fusiform [164] (tube-shaped). They have the potential to enlarge, rupture, or explode, resulting in severe injury or even death [165].

NEAT1 is an oncogenic lncRNA which is also reported to be upregulated in AAA [166]. NEAT1 overexpression leads to a reduction in the proliferation of the VSMCs and an increase in the apoptosis rates. Thus, NEAT1 contributes to the disease by promoting apoptosis of VSMCs and suppressing their proliferation for repair. NEAT1 was also shown to regulate the tubby-like protein 3 (TULP3) expression. NEAT1 acts like a microRNA sponge for miR-4688 and sequesteres it. This allows for higher expression of TULP3, as it is a target of miR-4688 [167].

In people with aortic aneurysms, the gene signal transducer and activator of transcription 3 (STAT3) is known to be upregulated [168]. This gene’s downregulation promotes cellular growth and prevents apoptosis. According to a report, the gene is targeted by miR-106b-5p. This miRNA is responsible for upregulating Bcl-2 while downregulating Bax (Bcl-2-Like Protein 4) and Caspase-3. Apoptosis is promoted by Bax and Caspase-3 whereas it is depressed by Bcl-2 [169]. This miR-106b-5p contributes to lowering the apoptotic rate [170]. The lncRNA SNHG16 is a ceRNA that spongs miR-106b-5p, leading to higher STAT3 expression. So SNHG16 promotes the disease by reducing the availability of miR-106b-5p, which leads to an increase in STAT3 expression [171].

**Role in brain disorders**

The role of miRNA-lncRNA-mRNA interrelationship in various neurological disorders is as follows:

**Parkinson’s disease**

Parkinson’s disease is a neurological condition that progresses. It makes the muscles tremble and spasm out of control. Dopaminergic loss of neurons in the substantia nigra and deregulation of basal ganglia neurons are two features of the disease [172].

It was discovered that microRNA miR-7 is downregulated and the lncRNA SNHG1 is increased in cultured microglial cells. In addition to SNHG1, microglial activation markers CD11b and Iba-1, as well as higher levels of inflammatory cytokines TNF-α, COX-2, IL-18, IL-6, and IL-1, were also detected. Their expression was correlated, indicating that SNHG1 [173] is at least partially responsible for controlling them.

Analysis of the SNHG1 sequence using miRcode showed (Table 3) a conserved miR-7 target site, and its role in downregulating miR-7 was proved. MiR-7 is a regulator of NLRP3 inflammasome [174]. NLRP3 inflammasome is one of the
most important contributors to the pathogenesis of the disease. SNHG1 overexpression increases the expression of NLRP3 at the transcript and protein level. This shows that downregulation of SNHG1 reduces the activation of microglia and reduces dopaminergic neuron loss.

Alzheimer’s disease

Alzheimer’s disease is a neurological ailment that worsens with time and causes the neurons to atrophy. Dementia, loss of social and behavioral facets of personality, and memory loss that gets progressively worse are the results of this. The abnormal buildup of a variety of different components in the brain and neurological system may be the cause of this. Apolipoprotein E (apoE), α-synuclein, Amyloid-β (Aβ) peptides, and tau are some of them [175].

According to reports, the disorder has an overexpression of IncRNA 17A. Apoptosis occurred at a noticeably lower rate in cells with reduced 17A expression, according to knockdown studies, demonstrating the importance of 17A in the process. It has also been demonstrated that 17A regulates the expression of the suggestive peptides Aβ40 and Aβ42 for the course of Alzheimer’s disease [176]. When 17A was knocked down, there was a lower amount of these peptides produced, while its overexpression led to their increase, indicating the progression of the disease. Overexpression of 17A also corresponded to lower GABABR2 (Gamma-Aminobutyric Acid Type B Receptor Subunit 2) protein expression, which is a cell-signaling receptor of the nervous system [177]. 17A overexpression also leads to a decrease in nestin-positive cells, indicating its role in the suppression of neurogenesis [175].

There is evidence that miR-206, a microRNA, is increased in Alzheimer’s disease. MiR-206 inhibits the expression of brain-derived neurotrophic factor (BDNF) by attaching to its 3’ UTR. For context, consider that when anti-miR-206 siRNA was delivered into the brain of Alzheimer’s model mice (Tg2576), the mice displayed improved spatial memory [178].

Schizophrenia

One of the most common, chronic brain conditions is schizophrenia [179]. Hallucinations, psychosis, delusions, mental disarray, and so on are some of the disease’s symptoms. It was discovered that miR-137 and schizophrenia are related. Two distinct (genome-wide association studies (GWAS) that involved participants in Sternberg item recognition paradigm (SIRP) working memory tasks implicated miR-137 [180]. MiR-137 had 26 experimentally confirmed targets. Grey matter density and cognitive function are assumed to be maintained by these genes [181]. In addition to miR-137, there were 3,859 differentially expressed (DE) mRNAs, 2400 DE IncRNAs, and 69 DE miRNAs in patients with disease [182]. 375 of these mRNAs were discovered to be involved in autophagy. There were not many DE RNAs associated with the MAPK, mTOR, and ErbB pathways.

A transcriptome analysis of schizophrenia patients and controls was carried out in a 2021 study. The discovered 12 DE mRNAs (BDNF, VEGFA, FGF2, FOS, CD44, SOX2, NRAS, SPARC, ZFP36, FGG, ELAVL1, and STARD13) are thought to be regulated by the reported 10 DE IncRNAs (DLX6-ASI, NEAT1, MINCR, LINC01094, DLGAP1-ASI, BABAM2-ASI, PAX8-ASI, ZFHX4-ASI, XIST, and MALAT1) [183].

CONCLUSION

In the control of cellular machinery, interactions among mRNAs, IncRNAs, and miRNAs are crucial. Several disorders are also thought to be impacted by these connections. Direct protein coding is provided by the mRNAs. The miRNAs either destroy mRNAs or stop their translation. To stop miRNAs from inhibiting mRNAs, IncRNAs act as a sponge for them. Only recently have researchers begun to examine the intricate interaction patterns of the miRNA-InRNA-mRNA network. As of now, our knowledge of this network is not complete. The interactome is being investigated, and more information is gradually becoming known. Many illnesses, such as strokes, atherosclerosis, Parkinson’s, and so on, were formerly believed to be inherited genetically or acquired through environmental factors. Nevertheless, we can now see that they can play quite an important role thanks to a greater knowledge of ncRNA-mRNA interaction. Using the creation and validation of powerful techniques like luciferase reporter assays, GWAS, and so on, we can confirm the interactions of these RNAs and validate them in vitro studies before in vivo investigations. The fundamental or traditional machine learning methods of disease-related miRNA tools provide important insights into the history and potential of miRNA tools.

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ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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