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Small "Non-Coding RNAs" (sncRNAs) and their Role in Gene Repression, Post-Transcriptional Gene Regulation and Therapeutics. Part-II: MicroRNA (miRNA); its Biogenesis, Role in Post-Transcriptional Gene Silencing (PTGS) and Therapeutic Applications

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Abstract: This review focuses on the microRNAs (miRNAs) which are single stranded and endogenously derived from non-coding RNA precursor. MicroRNAs function as guide molecules in mRNA silencing; targeting nearly all developmental and pathological processes in animals. The biogenesis and processing of miRNAs are under strict temporal regulation. The dysregulation of miRNAs in humans is associated with many diseases, particularly cancer. In animals, miRNAs are ~22 nucleotides long and are processed by two RNase III proteins- Drosha (in nucleus) and Dicer (in cytoplasm). MicroRNAs regulate cellular functions such as growth, development, differentiation, metabolism, and immune responses which are achieved by binding to the corresponding target mRNAs and inhibiting synthesis of notorious proteins. Apart of intracellular post-transcriptional gene regulation, miRNAs are also released into extracellular fluids (called circulating miRNAs) and have been observed to play roles in intercellular communications and regulations. miRNAs have been implicated as the good biomarker for the different types of cancers, inflammatory diseases and neurodegenerative diseases. Circulating miRNAs, because of its availability in extracellular fluids, are in easy access to the health personals to identify and diagnose the various types of diseases; and accordingly, miRNA based many diagnostic kits have been developed for the use. However, no miRNA-based drug has yet been approved for human use. Keeping in view of its wide potential and application for the humans, discovery of miRNA has credited the Nobel Prize of Physiology or Medicine to Victor Ambros and Gary Ruvkun for the year 2024.

Keywords: MicroRNA, Biogenesis, Microprocessor, Dicer, Processing, Therapeutic applications

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Introduction

RNAs are divided into two categories based on the translational potential: (i) RNAs with coding potential (i.e. mRNA); and (ii) RNAs without coding potential (also known as non-coding RNAs

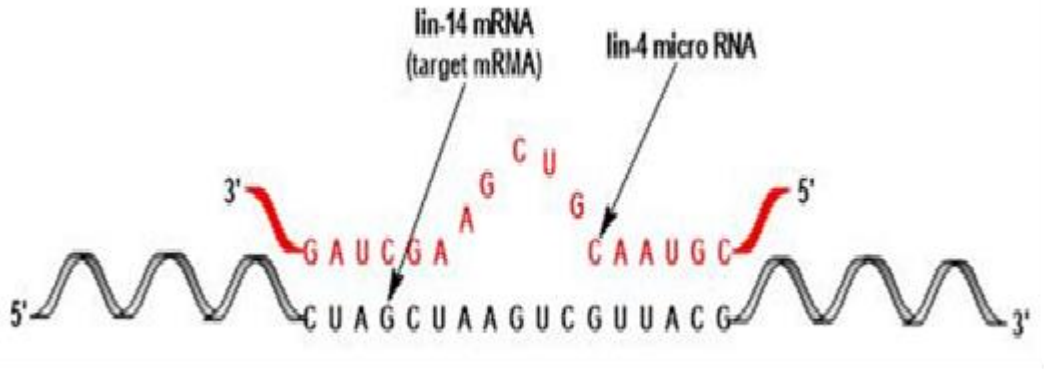


Fig. 1: Ambros and Ruvkun discovered that the *lin-4* gene encoded a tiny RNA (i.e., microRNA) that did not code for any protein. The *lin-4* microRNA sequence matched a complementary sequence in the target *lin-14* mRNA and blocks the protein synthesis of that RNA.

= ncRNAs). Non-coding RNAs (ncRNAs) were earlier thought to have no cellular roles hence regarded as "evolutionary junk"; but later, however, new researches have concluded that they have substantial functional roles to regulate the various molecular pathways either directly or through gene regulation.

Non-coding RNAs (ncRNAs), based on their length (i.e., number of nucleotides present in them) are further classified into two categories *viz.* (i) small non-coding RNAs (sncRNAs) which consist of a few to up to 200 nucleotides (nt); and (ii) long non-coding RNA (lncRNAs) which composed of more than 200 nucleotides (nt) up to several kilobases. Small non-coding RNAs includes small interfering RNAs (siRNA), microRNAs (miRNAs) and piwi interacting RNAs (piRNAs). This review deals primarily with biogenesis and therapeutic applications of microRNAs (miRNAs); however, the other two forms like siRNA and piRNA are reviewed elsewhere in this issue of journal.

Soon after the discovery that siRNAs (short exogenous dsRNA) are the effector of RNAi, it was shown that there is another class of endogenous RNA molecules of the same size in worms, flies, mice and humans called microRNA (miRNA) by Ambros (1989) and Ruvkun *et al.* (1989). These investigators while studying the genes that control the timings of (temporal) development of various cell types during the embryogenesis of the worm *C. elegans,* suggested that the *lin-4* gene appeared to be a negative regulator of the *lin-14* gene. However, the mechanism of how the *lin-14* activity was blocked remained unknown. In their later studies they concluded that the *lin-4* gene produced an unusually short RNA molecule that blocked the codes for protein production by *lin-14* gene (Rosalind *et al*., 1993). These surprising results suggested that this small RNA from *lin-4* was responsible for inhibiting *lin-14*. The *lin-4* sequence was observed to get matched with complementary sequence of the *lin-14* functional mRNA in the "critical segment", followed by blocking the production of *lin-14* protein (Lee *et al*., 1993; Wightman *et al*., 1993) (Fig. 1).

Later, Pasquinelli *et al*. (2000) published the discovery of another microRNA, encoded by the *let-7* gene of *C. elegans,* sequence of which, unlike *lin-4* gene, was highly conserved and reported to be present throughout the animal kingdom including humans. This discovery focussed the great interest, and later hundreds of different microRNAs were identified (Ruvkun *et al*., 2004; Bartel, 2018). Today, we know that there are more than a thousand genes in humans for different microRNAs. Further, it was established that gene regulation by microRNA is universal phenomena among multicellular organisms. Today, it is

estimated that about 30% of all genes are regulated by miRNAs (Bartel, 2004, 2018; Li *et al*., 2023).

The small miRNAs are processed from larger hairpin-like precursors by an RNAi-like machinery. The miRNAs can regulate gene expression by base-pairing to target mRNA, which results in either degradation of the target mRNA or suppression of its translation. Now, it is established that miRNAs play important roles during embryonic development of not only in *C. elegans* but in other higher animals including mammals (Bartel, 2018). Thus, the miRNA-dependent control of gene expression presents a new principle and can be explored for therapeutic and pathological purposes.

Yang *et al.* (2016) and Azam *et al*. (2024) reported that even though having structural and functional similarity, siRNAs and miRNAs have conspicuous differences-- (i) While siRNAs are derived from exogenous double-stranded RNA injected/transfected into the cells; microRNAs are derived from single stranded endogenous transcripts of non-coding RNA precursor. Hence, these differences make them useful for different purposes; (ii) siRNAs are specific for a single target mRNA; while miRNAs can have multiple mRNA targets (the numbers of target mRNA vary depending on the miRNA and the type of cells).

Biogenesis of microRNA

The biogenesis of miRNAs follows two pathways: (a) the intergenic (canonical processing) pathway, and (b) the intronic (non-canonical) pathway (MacFarlane and Murphy, 2010; Ha and Kim, 2014; O'Brien *et al.*, 2018; Azam *et al.*, 2024). The canonical pathway of biogenesis of miRNAs is under strict control and their dysregulation leads to the onset of diverse illness. In humans, canonical pathway of miRNA maturation is completed through two consecutive cleavage steps-- (i) In nucleus mediated by a heterotrimeric protein complex called Microprocessor, and (ii) In cytoplasm mediated by DICER, RISC and Argonaute proteins.

Processing in Nucleus by Heterotrimeric Microprocessor (*i.e., from new primary microRNA transcript to pre-microRNA*) (*Fig. 2*)

In nucleus, the initial long primary miRNA transcript (pri-miRNA transcript) is transcribed by RNA polymerase II with 5' cap and 3' poly-(A) tail. This primary transcript folds back on itself to form a long, double-stranded, hairpin-shaped RNA called a pri-miRNA, containing a stem, an apical hairpin loop of variable size at the apical junction and single-strand RNA (ssRNA) overhangs as a basal segment at the basal junction (Fig. 2). In nucleus, processing involves the heterotrimeric protein complex known as microprocessor, which consists of one molecule of Drosha protein and two molecules of DiGeorge Critical Region 8 (DGCR8) proteins (Haand Kim, 2014). In the nucleus, microprocessor causes site-specific cleavage of long primary microRNA transcript (pri-miRNA) to produce a hairpin precursor microRNA (pre-miRNA) of ~65-nucleotide in length with 2 nucleotides overhang at 3' end. Recent studies have identified that primary base sequence acts as the determinant in the pri-miRNA providing recognition site for microprocessor that contribute to specificity and efficiency of cleavage.

Drosha is a member of RNase III endonuclease family having highly conserved "central domain (CED)" essential for its cleavage activity. Further, its C-terminal segment containing two tandem RNase III domains (i.e., RIIIDa and RIIIDb) and one dsRNA-binding domain (dsRBD). The pair of RIIIDs dimerizes intra-molecularly to form a composite processing centre which exhibits the ability to cut the 3′ and 5′ strands of the pri-miRNA stem, thereby generating the characteristic staggered ends containing 2-nucleotides overhangs at 3′-end. The central RNA-binding heme domain (Rhed) of DGCR8 causes dimerization of RIIIDa and RIIIDb and maintains

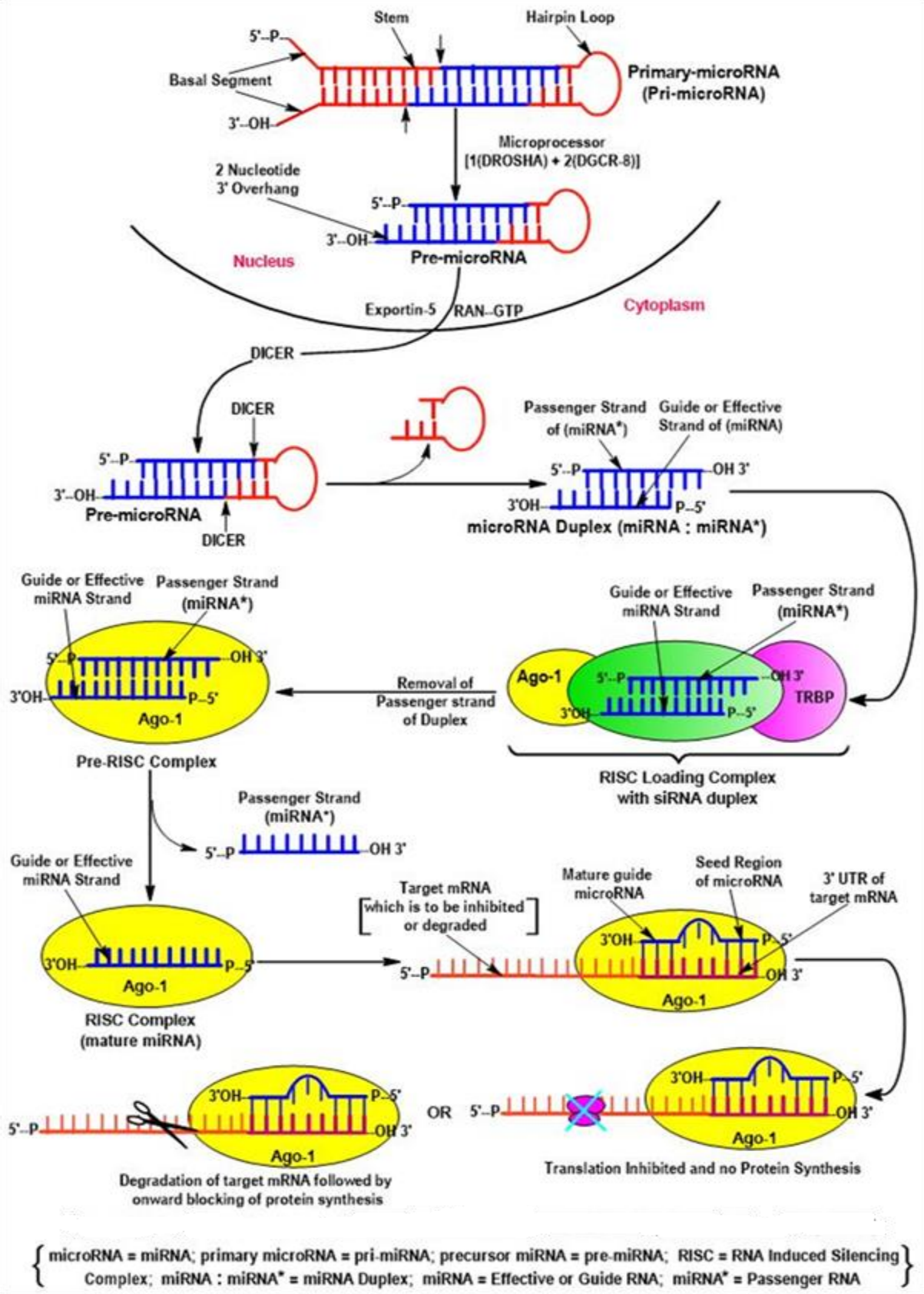


Fig. 2: Mechanism of post-transcriptional Gene inhibition or Gene Silencing through microRNA (miRNA).

BOX 1

In humans, exportin-5 (EXPO-5) is a protein which causes to export pre-microRNA from nucleus to cytoplasm. RAN (RAs-related Nuclear protein) also known as GTP-binding nuclear protein is essential for supporting the exportin-5 during the translocation of RNA through the nuclear pore complex. Ultimately, RAN-GTP complex together causes to transport (export) the pre-miRNA from nucleus to cytoplasm.

processing of pri-microRNA by microprocessor with accurate fidelity. The dsRBDs of Drosha have feeble RNA binding capacity, which is enhanced by dsRBDs of DGCR8, making microprocessor more competent and strong binding and processing complex. The C-terminal tail region (CTT) of DGCR8 is known to bind with and stabilize the Drosha. (See BOX 2 for structure and composition of Drosha and DGCR8). PAZ-like domains of Drosha could collaborate so as to not only serve as the catalytic subunit but also determine the cleavage sites by measuring the length of dsRNA (~11 bp) from the basal junction of pri-miRNA; thereby allowing the RIIIDa catalytic site to cut~11-bp away from the basal junction. The overall composition of Microprocessor has been depicted in BOX 2.

Processing in Cytoplasm (*by DICER, RISC and Argonaute proteins*)

After initial processing by microprocessor in nucleus, it yields the ~ 60-70 nucleotides long, loop having pre-microRNA duplex with 2 nucleotides overhangs at 3' end (Fig. 2). The pre-microRNA is exported out of nucleus with the help of protein exportin-5 (EXPO-5) which is facilitated by RAN-GTP complex. This export shuttles pre-microRNA into the cytoplasm for further processing to make the mature miRNA (for exportin-5 and RAN-GTP) (BOX 1).

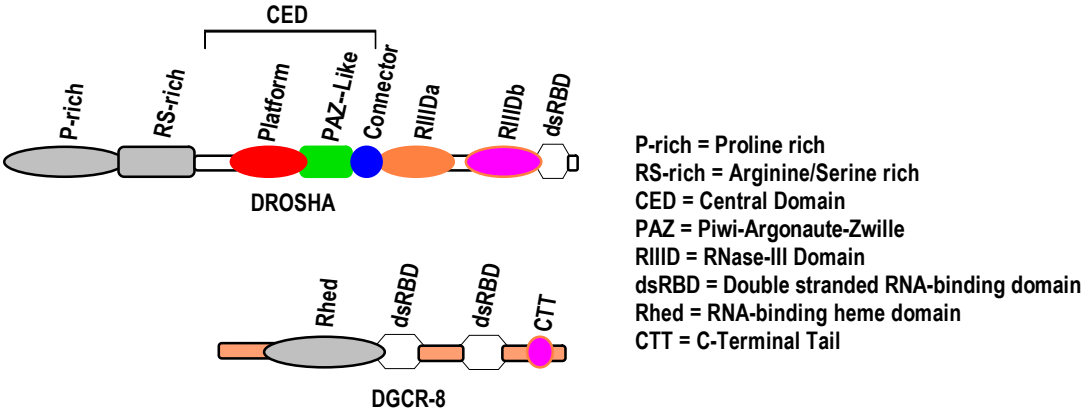
In cytoplasm, pre-miRNA undergoes another cleavage step by DICER protein (another endonuclease), liberating a ~22-nucleotide long miRNA duplex (miRNA : miRNA* duplex) removing loop region; thereby, still generating staggered ends containing 2-nucleotides overhangs at 3′ ends at both the strands. Of that duplex, one strand is known as effective or guide strand (miRNA), while other strand is called passenger strand (miRNA*). The duplex is now loaded to the RISC loading complex (composed of DICER, Ago-1 and TRBP) and named as "pre-RISC complex (preRNA Induced Silencing Complex)". Dicer is the same ribonuclease which is responsible for the formation of siRNAs. As with siRNAs, the effective guide microRNA strand (miRNA) remains loaded onto an Argonaute-1 protein; whereas, the other "passenger strand" (miRNA*) is displaced or dis-assembled. This results the formation of the complex of "single effective strand" and "Argonaute-1" protein which is now named RISC (RNA Induced Silencing Complex), also known as mature miRNA (Fig. 2). The effective strand of microRNA loaded into the silencing complex (RISC) guides the associated argonaute-1 protein to the close proximity to the target mRNA and makes complementary pairing to carry out sequence-specific inhibition of target mRNAs *via* inhibiting translation and/or its degradation. A typical miRNA in animal cells is partially complementary to a small portion in the 3′ UTR (3' Untranslated Region) of the target mRNA. In these cases, base-pairing involves six or seven nucleotides near the 5′ end of the miRNA (typically nucleotides 2–8 of the miRNA), which is referred to as the "seed region", as well as a few additional base pairs elsewhere in the miRNA. Unlike siRNAs, miRNAs that inhibit translation are only partially complementary to the target mRNA; hence, the small unpaired portion of that "bulges out". This step of regulation involves the adaptor protein Trinucleotide Repeat-Containing-6 (TNRC6) and the poly (A)-binding protein-C1(PABPC1) that recruit deadenylase complexes which starts de-adenylation of 3' poly (A) tail and shorten the mRNA, causing inhibition (for TNRC6 and PABPC1, see BOX 3).

BOX 2

Composition of Microprocessor

The Microprocessor consists of heterotrimeric protein complex with one molecule of Drosha and two molecules of DiGeorge Critical Region 8 (DGCR8). Drosha belongs to the RNase III endonuclease family. The critical domains of Drosha include-

(a) A highly conserved "central domain (CED)", which is essential for its cleavage activity.
(b) A C-terminal segment containing two tandem RNaseIII domains (RIIIDa and RIIIDb). The pair of RIIIDs dimerize intra-molecularly to form a unified processing centre with the ability to cut the 3′ and 5′ strands of the pri-miRNA stem, resulting to characteristic staggered ends with2-nucleotides (2-nt) 3′-overhangs.
(c) One dsRNA-binding domain (dsRBD). The dsRBDs of Drosha have weak RNA binding capacity. The binding affinity of Drosha gets increased by DGCR8.
(d) The PAZ (Piwi/Argonaute/Zwille) domain present in Drosha is responsible for recognition of a2-nucleotides overhang at the 3′ end of double-stranded RNA (dsRNA), as well as recognition of the 3′ end of single-stranded RNA (ssRNA). In eukaryotes, the PAZ domain is found in proteins of Argonaute (Ago) and Piwi subfamilies; and also, in the RNase III ribonucleases family like Drosha and DICER.



Structure of DROSA and DGCR-8

DiGeorge Critical Region-8 (DGCR8) is a double-stranded RNA-binding protein which associates with Drosha and facilitates microRNA (miRNA) maturation. DGCR-8 have--

(a) The Central RNA-Binding Heme Domain (Rhed) which contributes to dimerization and maintains the fidelity of microprocessor during processing.
(b) The Double Stranded RNA Binding Domains (dsRBDs) which is responsible for higher binding affinity to RNA.
(c) The C-Terminal Tail (CTT) region is a helical structure which causes its attachment with Drosha to stabilize that.

Hence, drosha and DGCR8 together form a complex termed microprocessor. However, Drosha alone appears to have a weak RNA-binding capacity, and DGCR8 alone does not have a sufficient specificity to distinguish the substrates. This yields conclusions that multiple domains in Drosha and DGCR8 together contribute to the recognition of, binding with and also trimming of the pri-microRNA from specific point during its maturation.

MicroRNA was first discovered by Victor Ambros and Gary Ruvkun while doing works on a nematode worm *Caenorhabditis elegans* (*C. elegans*). In their experiments on *C. elegans,* they found that the short non-coding microRNA (~22 nucleotide long) transcribed by *lin-4* gene could successfully inhibit the translation of the target mRNA transcribed by *lin-14* gene and cause the

BOX 3

Trinucleotide repeat-containing-6 (TNRC6) protein functions in post-transcriptional gene silencing through the RNA interference (RNAi) and microRNA pathways. The protein associates with messenger RNAs and Argonaute proteins. Poly(A)-binding protein cytoplasmic-1(PABPC1) is a cytoplasmic poly(A)-binding protein (PABP) that plays a role in mRNA degradation. TNRC6 and PABPC1 recruit deadenylase to regulate the length of the poly(A) tail and hence, mRNA stability too. De-adenylation is a major step in mammalian mRNA decay which involves the hydrolysis of poly(A) tail of target mRNA in the 3′→5′ direction by deadenylases. Deadenylases are Mg^{2+} dependent exoribonucleases, main substrate of which is poly(A) tails. Once the poly-A tail is hydrolysed and removed, other degradative enzymes initiate the degradation of the mRNA. De-adenylation complex is recruited through interactions of TNRC6 with PABPC1. Alternatively, they can be recruited to specific mRNAs through interactions with sequence-specific RNA-binding proteins or the microRNA machinery.

developmental defects. They further studied its biogenesis and concluded about its role and mechanism of post-transcriptional gene regulation (post-transcriptional gene inhibition); for which, Victor Ambros and Gary Ruvkun were awarded Nobel Prize of Physiology or Medicine for the year 2024.

Non-canonical processing (intronic pathways) is an alternative pathway for miRNA biogenesis without involving Drosha or Dicer. At the place of Drosha/DGCR8 and Dicer, non-canonical miRNA biogenesis is processed by a variety of proteins that are the integral part of the conventional pathway, such as exportin 5, exportin 6, and AGO2. Non-canonical processing pathways are less understood than the canonical pathway, and their roles in miRNA biogenesis and gene regulation are still being investigated (Azam *et al.*, 2024).

This is to be taken into notice that siRNAs and microRNAs are processed through DICER dependent routes (steps).

Significance of miRNA

To highlight the fundamental role of microRNAs, it is important to note that the most microRNA genes function early in embryonic development; whereas, microRNAs that evolved specifically in mammals, function at later stages of embryonic development (DeVeale *et al.*, 2021). In contrast, many species-specific microRNA genes generally play roles in adult cell-types rather than in embryonic development. These patterns are substantiated by the systematic knockout experiments on microRNA genes with varied evolutionary conservation.

Therapeutic Significance

MicroRNAs regulate cellular functions such as growth, development, differentiation, metabolism, and immune responses which are achieved by its binding to the corresponding target mRNA and inhibiting protein synthesis in the post-transcriptional phase (O'Brien *et al.*, 2018). The development and progress of human diseases are affected by miRNAs; which are also essential for regulating drug metabolism and immune responses (Wang and Chen, 2021).

Apart of intracellular post-transcriptional gene regulation, miRNAs are also released in to extracellular fluids and have been observed to play roles in intercellular communications (Arroyo *et al.*, 2011; Vickers *et al.*, 2011; Ho *et al.*, 2022). MicroRNAs transported outside the cells and entering into the body fluids are called circulating miRNAs (Weber *et al.*, 2010). Their presence in body fluids and easy accessibility can be explored as non-invasive diagnostic techniques using them as biomarker for many diseases (Diener *et al.*, 2022; Editorial, Nature Biotechnology, 2024). Circulating miRNAs can be further divided into two categories-- (i) miRNAs complexed with the proteins [like Ago2 and NPM-1(Nucleophosmin-1)] and high-density lipoprotein; which constitute approximately 90% of circulating miRNAs, and (ii) The remaining 10% are packed in exosomes and secreted outside of cells (Ho *et al.*, 2022). The packaging in exosomes or forming complex with

proteins is essential to prevent miRNAs degradation by RNases present in body fluids. Exosome which contains miRNAs may enter neighbouring cells through endocytic uptake, membrane fusion, or integrating with specific cell surface receptors and affect remotely placed mRNA targets from their origin (Morello *et al*., 2013). Many workers have observed the presence of extracellular/circulating miRNAs in biological fluids (such as plasma and serum, cerebrospinal fluid, saliva, breast milk, urine, tears, colostrum, peritoneal fluid, bronchial lavage, seminal fluid, and ovarian follicular fluid). In neurodegenerative diseases, cerebrospinal fluid may be beneficial over detecting blood-based miRNA biomarkers owing to the presence of the blood–brain barrier.

Circulating microRNAs are now considered as promising biomarkers for many human diseases because of their high specificity, easy accessibility, and sensitivity. These are also specific for certain tissue or cell types. For example, some miRNAs (e.g. miRNA-122-5p) are highly abundant in hepatic cells; while others (e.g. miRNA-140) are cartilage-specific. This feature found strong possibility of using specific miRNAs to determine the initiation and progression of a disease (Ho *et al*., 2022). The sensitivity of miRNAs has been studied and found that their levels can vary (upregulated or downregulated) in accordance with disease initiation, progression or with response to therapy. With these advantages, miRNAs give a non-invasive method for accurate diagnosis and prognosis (understanding the future progression or regression of disease) to guide treatment, as well as evaluating effectiveness to treatment.

In humans, mutations in specific microRNA genes or components of the biogenesis pathway are associated with the various types of syndromes. For example, mutation in the DICER-1 gene, results in tumours in the kidney, thyroid, ovary, cervix, testicle, brain, eye, and lung; which is called DICER syndrome. Though the base-pairing portion (i.e., the seed region) of individual microRNA genes is very short (posing very less chance of mutations); even then, there are certain mutations in the seed sequence of specific microRNA genes linked to a disease result in progressive loss of hearing. Some other diseases are EDICT syndrome (a rare ophthalmic disease with hypoplasia of iris); endothelial dystrophy; congenital cataract and congenital skeletal disorder related with the mutation in miRNA gene (Azam *et al*., 2024). Since circulating miRNAs are easily accessible in body fluids, it is used as a pathological biomarker to diagnose the different diseases. Accordingly, some microRNA-based diagnostic kits have been developed; and still trials are being done for developing more diagnostics and therapeutics for different diseases *viz.* metabolic disorders, cardiovascular disease, neurodegenerative conditions, and cancer (Kim *et al*., 2023).

miRNA has important role in three major human diseases *viz.* cancer, inflammatory disease, and neurological disease**;** which collectively share the higher percentage of disease burden and challenges. Although each category covers a large spectrum of disorders; here, author focuses on a core set of miRNAs with its substantiated roles in pathogenesis across these categories.

The multi-target regulatory potential of miRNAs provides a much effective therapeutic strategy by more than what is the "one gene – one disease" principle, and makes miRNA-based therapies a demanding strategy for precision medicine (Quah *et al.*, 2025).

(A) *miRNA and Cancer*:

Cancer is a condition resulting from the unchecked proliferation of individual cells after losing the regulatory control over cell division; which may either be (i) metabolic disturbances due to activated signal transduction proteins or (ii) dysregulated miRNAs (Yong and Croce, 2016). It has been reviewed few researchers (Ho *et al*., 2022; Menon *et al*., 2022; Quah *et al*., 2025) that some miRNAs get dysregulated (either upregulated or downregulated) during cancer; and becomes a conspicuous symptom to be used

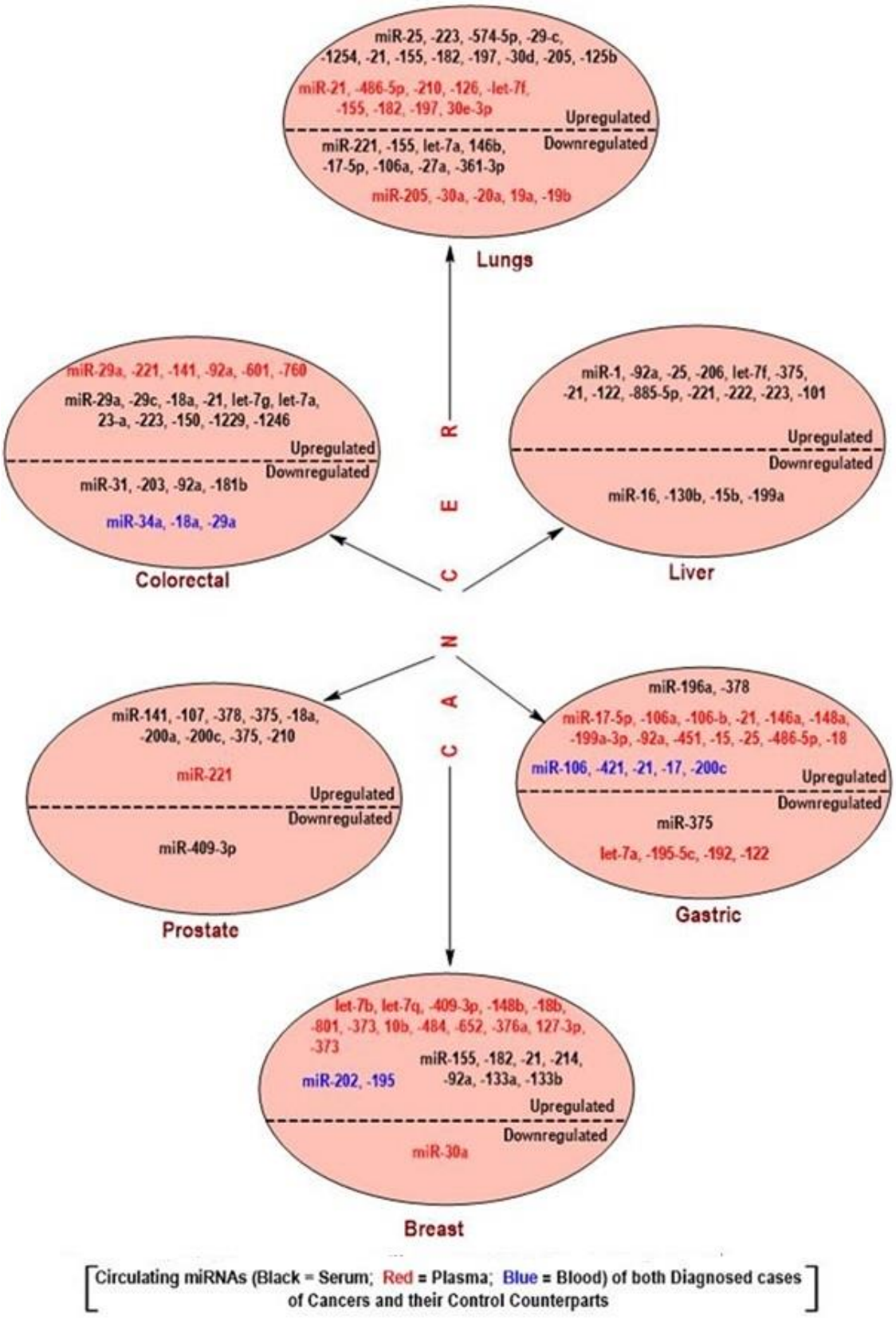


Fig. 3: Circulating miRNA biomarker in some cancerous conditions. Figure shows levels (upregulated and downregulated) of different miRNA during the cancer.

as biomarker. A brief summary of the types and level of circulating miRNAs in plasma, serum, and blood samples in lung, prostate, breast, colorectal, gastric, and liver cancers due to their dysregulation have been depicted in Figure 3.

Further, miRNAs can be used as promising prognostic markers to assess the efficacy of anticancer drugs; as their altered levels can be used to predict the efficacy/response of chemotherapy and disease recurrence (Ho *et al*., 2022). For example, a few conditions are as follow:

(a) In breast cancer, upregulation of miR-125b and miR-210 can reveal a lower therapeutic response and resistance to certain drugs and cause the tumour development.

(b) In prostate cancer, upregulation of miR-21 is associated with the resistance to drug "docetaxel"; and also elevated levels of three miRNAs (miR-141, -146b-3p, and -194) are the indicator of rapid biochemical recurrence and the increased level of prostate-specific antigen (PSA) in blood of prostate cancer patients undergoing radiation therapy and/or surgery.

(c) In colorectal cancer, five serum miRNAs (miR-20a, -130, -145, -216, and -372) were positively correlated to sensitivity/ resistance to chemotherapy.

(d) Similarly, in lung cancer, four types of miRNAs (miR-486, -30d, -1 and -499) were correlated to the survival of non-small cell lung cancer (NSCLC) patients undertaking surgery or/and chemotherapy.

(B) *miRNA and Inflammatory Diseases*:

Inflammation is the initial response of immune system against any injury and infection. Many human pathological conditions are associated with chronic inflammation, autoimmunity, or both. MicroRNAs are implicated as the integral feature of regulatory networks of both the innate and adaptive immune responses (Quah *et al*., 2025).

miR-155 and miR-146a play crucial role in inflammatory diseases. miR-155, is so related to inflammatory response that it is given synonym as 'master regulator of inflammation'; whereas, miR-146a is associated with adaptive immunity (Mahesh and Biswas, 2019). miR-146a was identified with miR-155 as part of a group of miRNAs that are upregulated in response to endotoxins (Carpenter and O'Neill, 2024). Endotoxin, also known as lipopolysaccharide (LPS), is a component of the outer membrane of Gram-negative bacteria and is released when bacteria die or are lysed. It is a potent pyrogen (i.e., it can trigger fever and other inflammatory responses when it enters the bloodstream).

Mammalian miR-155 recorded prominently in a large number of inflammatory diseases, including pathological neuroinflammation (Mahesh and Bishwas, 2019). Inflammatory stimulation in innate and adaptive immune cells rapidly upregulates miR-155 by enhancing proinflammatory nuclear factor κB (NF-κB) signalling. miR-155 maintains proliferative activity in T-lymphocyte sub-sets and increases the development of inflammatory T helper cell subsets. B-cell maturation also requires miR-155. B-cells in absence of miR-155 failed to generate high-affinity immunoglobulin-1 (IgG1) antibodies (Azam *et al*., 2024).

Further evidence for miR-146a-mediated suppression of the acute immune response comes from studies on miR-146a and miR-155 in T cell-mediated immunity. miR-146a suppresses the antitumor response and interferon-γ (IFN-γ) secretion; whereas, miR-155 exhibits opposite epistatic effects over miR-146a. While miR-155 gets elevated in age-related chronic inflammation, overexpression of miR-146a reduces NF-κB pathway activation. These observations may explain the rapid initiation of the macrophage inflammatory response *via* miR-155 mediated enhancement of NF-κB signalling, followed by its resolution mediated by miR-146a (Carpenter and O'Neill, 2024; Quah *et al*., 2025). For example,

Table 1: Certain miRNA-based kit developed for clinical applications

Diagnostic Kit	Applications
miRviewTM Mets	For detecting cancers of unknown/ or uncertain origin.
RosettaGX Reveal	It is designed for distinguishing between indeterminate or benign thyroid nodules.
ThyraMir	Designed for identifying of thyroid cancer.
CogniMIR	It is in clinical trial for early diagnosis of Alzheimer's disease.
OsteomiR	It is designed for checking the hazard of a first fracture in type-2 diabetes and postmenopausal osteoporosis females.
ThrombomiR	Designed for assessing platelet function.

some effects of a few miRNAs on inflammatory conditions are given as follow:

miR132 = Provide resolution of inflammation during wound healing; negative effects on NF-kB signalling and cytokine/chemokine secretion.

miR21 = Modifies the overall inflammatory conditions; conditional (positive or negative) effects on inflammation.

miR155 = Activates and sustains inflammation and NF-kB signalling; enhances T and B-lymphocytes maturation; also, effective in anti-tumour immunity.

miR146 = Provide resolution of inflammation; negative effects on activation of NF-kB pathway.

(C) *miRNAs and Neurological Disorders*:

For human neurological disorders, circulating miRNAs were reported to be potential markers for diagnosis and prognosis (Azam *et al*., 2024). In Alzheimer's disease, a total of seven plasma circulating miRNAs (miR-545-3p, -301a-3p, -191-5p, -142-3p, -15b-5p, let-7g-5p, and let-7d-5p) could get detected patients with 95% accuracy from healthy donors (Kumar *et al*., 2013). The effects of miR-124 on neuroinflammation and neurodegeneration are primarily mediated through its influence on microglia (Li *et al*., 2023). miR-124 is a key regulator of microglial activation state (Quah *et al*., 2025). Exosomal delivery of miR-124 from neurons to microglia down-regulates microglial activation and neuro-inflammation. miR-124 downregulation and consequent neuroinflammation also features in the pathogenesis of Parkinson's disease and Alzheimer's disease. Microglia are a type of glial cell (non-neuronal cells) located throughout the brain and spinal cord of the central nervous system (CNS). Microglia are the key cells in overall maintaining the brain –by constant scavenging the plaques, damaged or unnecessary neurons and synapses, and infectious agents.

Further, there is no miRNA-based drug approved for any disease of human use, but many

are under different stages of clinical trial. However, till date some miRNA based diagnostic kits have been developed for the use as a clinical tool (Table 1).

Ethical Statement

This is a review article hence no Ethical Approval needed.

Conflict of Interest

The author declares no conflicts of interest.

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