

**Biogenesis and Function of miRNAs and Their Role in Cancer****Yustina Nuke Ardiyan<sup>1</sup>, Johana Puspasari Dwi Pratiwi<sup>2</sup>**

Universitas Kristen Duta Wacana, Indonesia

yustina.nuke@gmail.com

**Keywords**Small RNA, miRNA,  
mRNA, cancer**Abstract**

MicroRNA (miRNA) is a small RNA molecule that regulates post-transcriptional gene expression. miRNA combines with the RNA-induced silencing complex (RISC) and carries out its function in controlling translation. The formation of miRNA involves enzymes and proteins that cut it in its processing as well as protein complexes in the cytoplasm that make the miRNA mature. Several changes, for example deletion or overexpression, can occur in miRNAs, causing cancer growth. The aim of this study was to investigate the process of miRNA biogenesis as well as analyze how changes in miRNA expression can affect the biological pathways involved in cancer. This type of research is a literature review. The data that has been collected is then analyzed in three stages, namely data reduction, data presentation and drawing conclusions. The results show that the role of miRNAs is in the post-transcriptional regulation of genes. MiRNAs associate with the RISC complex and interact with mRNA through complementary base pairing thereby halting translation and promoting mRNA degradation. MiRNAs are deregulated in cancer, including over-expression of oncogenic miRNAs or deletion of miRNA characteristics as tumor inhibitors. The results of this research also provide a foundation for further education and advanced research in the field of molecular biology, particularly in genetic regulation and disease mechanisms.

Corresponding Author: Yustina Nuke Ardiyan

E-mail: [yustina.nuke@gmail.com](mailto:yustina.nuke@gmail.com)**INTRODUCTION**

There are various classes of *small endogenous RNA molecules*, including tRNA, rRNA, snoRNA, miRNA, and siRNA (Pangarsa et al., 2023). tRNA and rRNA function in the translation process. snoRNA plays a role in rRNA modification. miRNAs and siRNAs are biochemically and functionally indistinguishable. Both have 19-20 base pairs of nucleotides and combine with RISC to stop gene expression (Kumar et al. 2019).

miRNAs are small RNA molecules that regulate gene expression by base pairing with certain mRNAs and reducing their stability and translation into proteins. In humans, miRNAs are thought to regulate the expression of at least one third of the genes encoding proteins (Alberts *et al.*, 2014). Many studies have studied and discovered hundreds of types of miRNA and their role in cell metabolism and even in the incidence of cancer (Suryani, 2020).

MicroRNA (miRNA) is a small RNA molecule that plays a role in posttranscriptional regulation of gene expression. miRNAs bind to the RNA-induced silencing complex (RISC) to inhibit or reduce the mRNA translation process. The formation of miRNA involves a processing process in which enzymes and proteins such as Drosha, DGCR8, and Dicer play an important role in cutting the miRNA precursor into a mature form that is ready to function. In the cytoplasm, mature miRNAs combine with a protein complex within the miRISC, which includes Ago2, TRBP, and PACT, to target specific mRNAs and control gene expression.

Changes in miRNA expression, such as deletion or overexpression, can have a significant impact on genetic regulation and biological mechanisms. In the context of cancer, these changes may lead to dysfunction in the regulation of certain genes related to cell growth and metastatic processes. For example, certain miRNAs that normally act as tumor suppressors may experience reduced expression, while miRNAs that act as oncogenes may experience increased expression.

Many studies have studied and discovered hundreds of types of miRNA and their role in cell metabolism and even in the incidence of cancer (Suryani, 2020). Previous research by (McFarlane & Murphy, 2010) showed that the regulatory function of microRNAs is achieved through the RNA-induced silencing complex (RISC). MicroRNAs assemble into RISC, activating the complex to target the messenger RNA (mRNA) specified by the microRNA. Various models of RISC assembly have been proposed and research continues to explore the mechanisms of RISC loading and activation.

The degree and nature of complementarity between the microRNA and the target determines the mechanism of gene silencing, slicer-dependent mRNA degradation, or slicer-independent translational inhibition. Recent evidence suggests that P-bodies are essential for microRNA-mediated gene silencing and that RISC assembly and silencing occurs primarily within P-bodies. The P-body model describes microRNA sorting and switching between specialized P-body compartments housing enzymes required for slicer-dependent and slicer-independent silencing, addressing the reversibility of this silencing mechanism. Detailed knowledge of microRNA pathways is essential to understand their physiological roles and the implications associated with dysfunction and dysregulation.

The results of this study provide a strong foundation for further education and advanced research in the field of molecular biology, especially related to genetic regulation and disease mechanisms. A deeper understanding of the biogenesis and function of miRNAs and their role in cancer provides valuable insights for scientists and educators in elucidating the complexity of the biological pathways involved in disease progression. These findings not only support the development of novel miRNA-based therapies, but also stimulate further exploration of the possible applications of genetic technology in specific and precision medicine. The aim of this study was to investigate the process of miRNA biogenesis as well as analyze how changes in miRNA expression can affect the biological pathways involved in cancer.

## RESEARCH METHODS

This type of study is Literature Review. Keywords used to look for source articles namely “small RNA”, “miRNA”, “mRNA”, and “cancer”. Search article searched for from Google Scholar. Year article taken is from 2010 to 2023. Study conducted is with a narrative review. This research was carried out in 2023 for 4 days. The data that has been collected is then analyzed in three stages, namely data reduction, data presentation and drawing conclusions.

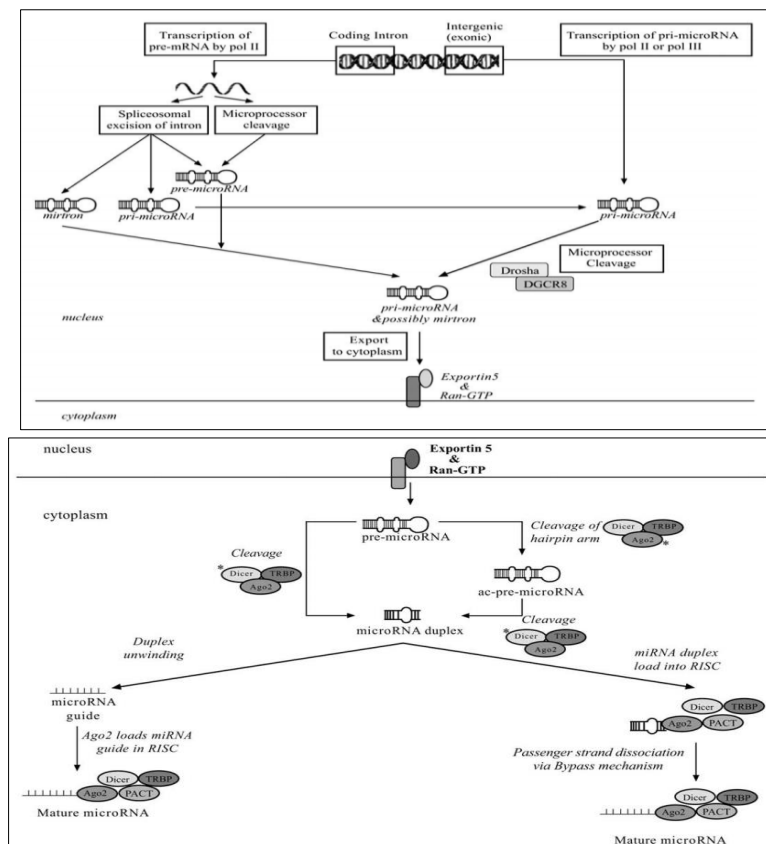
## RESULTS AND DISCUSSION

Based on the results of the literature search, 22,661 articles were found. By using keywords such as “small RNA”, “miRNA”, “mRNA”, and “cancer”. researchers can access thousands of scientific articles related to this topic. This search will yield a list of articles covering various aspects of miRNA biogenesis, their function in genetic regulation, and their critical role in various types of cancer. From these search results, researchers can then identify the most relevant and high-quality articles to serve as the main data source in their research. By collecting and analyzing data from around 20 of the most relevant and trusted articles, researchers can build a solid foundation of knowledge to support research objectives.

### Biogenesis of miRNAs

The process of forming miRNA after transcription consists of two steps, namely cutting in the nucleus and cytoplasm respectively, which is carried out by ribonuclease III endonuclease, namely Drosha and Dicer. The miRNA gene is transcribed into *primary*

miRNA (pri-miRNA) then processed again into precursor miRNA (pre-miRNA), then miRNA *duplex*. miRNA will combine with RISC to become miRISC which can carry out the function of controlling gene expression (Kurozumi et al. , 2016) .



**Figure 1. Nuclear and cytoplasmic components in the formation of miRNA (source: Macfarlane and Murphy, 2010)**

The DNA sequence that will be transcribed as miRNA is found in the intergenic region and intron of a gene (coding *intron*). Previously, these areas were called 'junk DNA' because their function was not yet known. miRNA precursors are less commonly found in exons. miRNAs originating from intergenic areas are transcribed by RNA polymerase II or III to produce pri-miRNA molecules (Bryson, 2021) . Pri-miRNA is processed into pre-miRNA by a *microprocessor complex* consisting of DGCR8 and Drosha. Pre-miRNA is carried out of the nucleus into the cytoplasm by nucleocytoplasmic transporter proteins, namely Exportin 5 and Ran-GTP. (Paisal & Kusmardi, 2023) . miRNAs contained in introns are transcribed by RNA polymerase II. After pre-mRNA is formed, *splicing* of introns occurs. One hypothesis states that after *splicing* pri-miRNA is produced, which is then cut by Drosha and DGCR8 to become pre-miRNA. Another hypothesis states that as a result of *splicing*, mirtron is formed, namely a miRNA molecule that does not undergo *microprocessor cleavage* and is directly transported outside the nucleus. Another hypothesis states that pre-miRNA is directly produced from pre-mRNA via *microprocessor cleavage*.

In the cytoplasm, the pre-miRNA is cleaved by Dicer to produce a *duplex miRNA*. miRNA can also be cleaved by Ago2 to produce *Ago2-cleaved precursor miRNA* (ac-pre-miRNA) which then becomes a substrate for Dicer (Angelina & Kodariah, 2016) . miRNA *duplex* releases mature miRNA to combine with RISC to become miRISC (Angelina & Kodariah, 2016) . The protein complex in miRISC is Ago2, TRBP, PACT, and Dicer.

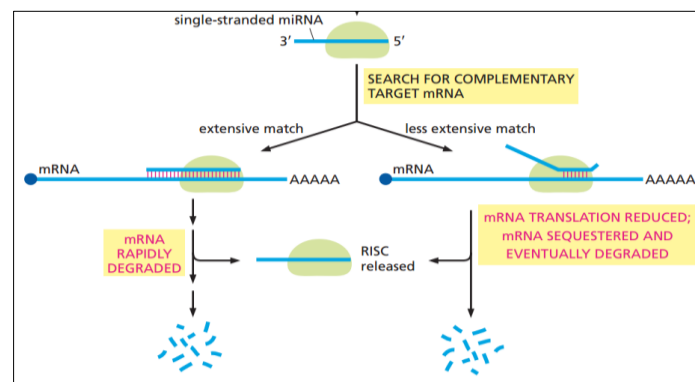
miRNAs, which were initially thought to originate from “junk DNA” or non-coding regions of the genome, are now recognized as key components in the post-transcriptional regulation of genes. The discovery that the DNA sequences that produce miRNAs are found in intergenic regions and introns of a gene (coding introns) illustrates the importance of these regions in complex genetic regulation. The process of miRNA biogenesis begins with

transcription by RNA polymerase II or III, depending on its genomic location. MiRNA produced from intergenic regions will be transcribed into pri-miRNA, which is then processed into pre-miRNA by a microprocessor complex involving DGCR8 and Drosha. Pre-miRNA is then transported from the nucleus to the cytoplasm by the Exportin 5 and Ran-GTP complex.

Meanwhile, miRNA originating from introns is transcribed together with pre-mRNA, and after the intron splicing process, can produce pre-miRNA. There are several hypotheses regarding this process, including the formation of mirtrons which are miRNAs that do not require processing by the microprocessor complex and can be directly exported from the nucleus. In the cytoplasm, pre-miRNA or pre-miRNA is cleaved by the Dicer enzyme into duplex miRNA. This process is important because mature miRNAs will be integrated into the RISC complex (RNA-induced silencing complex), which consists of proteins such as Ago2, TRBP, PACT, and Dicer. The RISC complex mediates the functional effects of miRNAs by targeting complementary mRNAs, terminating mRNA translation, or directing mRNA degradation.

### miRNAs as post-transcriptional regulators

miRNAs play important roles in many biological pathways in mammals and multicellular organisms (Mulyandarini, Rahman, & Adelina, 2022). MiRNAs influence cancer-related processes such as proliferation, cell cycle control, apoptosis, differentiation, migration, and metabolism. One miRNA molecule can target multiple mRNAs. Mature miRNA induces *posttranscriptional gene silencing* along with RISC (Salinah & Wuyung, 2019).



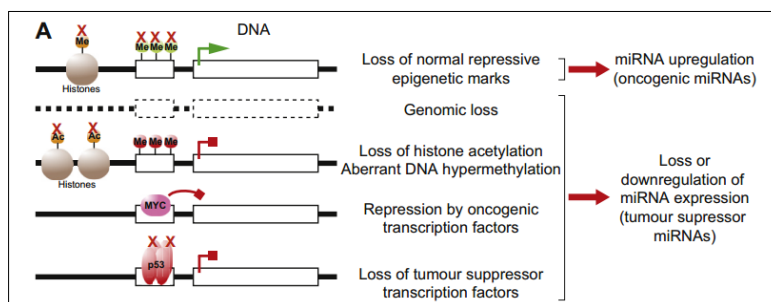
**Figure 2. miRNAs target complementary mRNA molecules for destruction**  
(source: Alberts et al, 2012)

miRISC will look for mRNA that has a nucleotide sequence that is complementary to the miRNA it binds to. If the complementary region is very long, the mRNA will quickly be degraded by the nucleases in miRISC. If the complementary region is short, translation stops and the mRNA is transported to an area in the cytoplasm where other cellular nucleases destroy it. The mRNA molecule has a short half-life in the cytoplasm, therefore if there is no translation the poly A tail at the 3' end continues to shorten making the mRNA unstable and ultimately degraded (Alberts *et al.*, 2014).

MiRNAs are known to influence various important aspects of genetic regulation, such as cell proliferation, cell cycle control, apoptosis, cell differentiation, cell migration, and metabolism. The ability of a single miRNA molecule to target multiple mRNAs indicates the significant complexity of genetic regulation governed by miRNAs. The process of miRNA biogenesis, in which mature miRNA induces posttranscriptional gene silencing via the RISC complex, also illustrates the fundamental mechanism of how miRNAs influence gene expression. MiRISC functions to search for mRNA that has a nucleotide sequence that is complementary to the miRNA it binds to. When the complementary region is long enough, the mRNA can be rapidly degraded by nucleases in miRISC, whereas if the complementary region is short, translation of the mRNA stops and the mRNA can be transported to other cytoplasmic regions for further degradation.

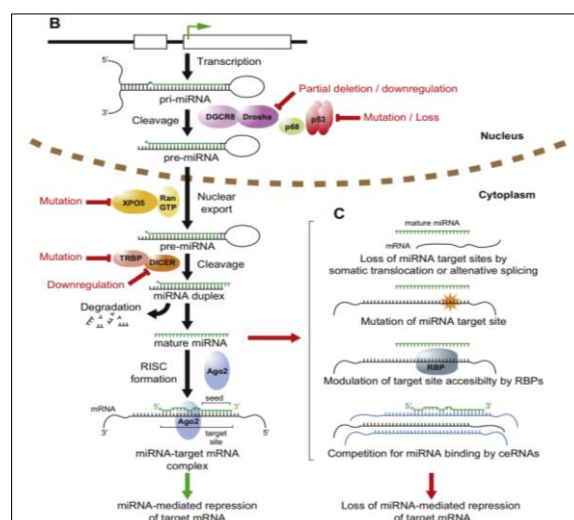
### The role of miRNAs in cancer development

miRNAs can function as tumor suppressors or as oncogenic factors. MiRNA dysregulation is demonstrated in many cancer events. Deletion of miRNA genes as tumor suppressors and amplification of miRNAs as oncogenic factors play a role in the development of cancer (Wang and Luo, 2015) .



**Figure 3. Deregulation of miRNA gene transcription in cancer through genetic, epigenetic and transcriptional mechanisms**  
 (source: Jansson and Lund, 2012)

miRNAs can be deregulated in cancer development. Demethylation causes genes that are not normally expressed to become expressed. As a result, miRNAs are upregulated and are oncogenic. miRNA will suppress the expression of *tumor suppressor genes* so that cancer develops. Downregulation of miRNAs which causes low miRNA expression is caused by gene deletion, loss of histone acetylation, DNA hypermethylation, suppression by oncogenic transcription factors (e.g. Myc), and loss of the p53 transcription factor (Peng and Croce, 2016) .



**Figure 4. Multiple defects in miRNA processing and escape of mRNA from miRNA regulation**  
 (source: Jansson and Lund, 2012)

Several mutations or deletions in genes that play a role in miRNA processing can cause the miRNA to not be expressed or have reduced function (Anwar, Haryono, Aryandono, & Haryana, 2018) . These disorders include deletion of the Drosha, p53, and Dicer genes. Mutations can occur in the p53, XPO5, and TRBP genes. Apart from mutations or deletions, mRNA can also escape miRNA regulation. The target sequence in mRNA can change due to somatic translocation, *alternative splicing*, or mutation. The presence of *RNA binding protein* (RBP) and *competitive endogenous RNA* (ceRNA) means that the miRNA cannot attach to the target mRNA and ultimately the regulation of the miRNA cannot take place (Kamali et al., 2024).

### **Oncogenic and tumor suppressive miRNAs in breast cancer**

miR-21 is a type of oncogenic miRNA. In breast cancer, miR-21 is overexpressed and suppresses *tumor suppressor genes*. Several studies confirmed that miR-21 is associated with cancer clinical stage, metastasis, and poor prognosis (Harahap, 2019). The target genes of miR-21 include *tumor suppressor tropomyosin 1* (TPM1), *programmed cell death 4* (PDCD4), *TIMP metalloproteinase inhibitor 3* (TIMP3), and *phosphatase & tensin homolog* (PTEN) (Wang and Luo, 2015).

TPM1 is an actin-binding protein involved in the regulation of tethering-independent growth and microfilament organization. miR-21 suppresses TPM1 resulting in changes in cytoskeleton structure that lead to neoplastic development, cell invasion, and metastasis. PDCD4 is a protein associated with apoptosis and regulation of urokinase receptor (uPAR) which is involved in extracellular matrix degradation. Suppression of PDCD4 causes progression to cancer (O'Bryan et al., 2017). TIMP3 is a gene that encodes a *matrix metalloproteinase inhibitor protein*. Metalloproteinases are a class of peptidases that cause degradation of the extracellular matrix. Suppression of miR-21 causes cancer metastasis to occur. PTEN works together with *phosphoinositide 3 kinase* (PI3K) in balancing levels of *phosphatidylinositol phosphate 3* (PIP3) which controls the Akt pathway. PTEN dephosphorylates PIP3 and PI3K phosphorylates PIP2 to maintain PIP3 balance. Suppression of PTEN by miR-21 increases PIP3 accumulation resulting in excessive stimulation of the Akt pathway, resulting in continuous growth (Wang & Luo, 2015).

#### **Let-7 family**

Let-7 is a miRNA that suppresses tumors (Angelina & Kodariah, 2016). In cancer, let-7 is deleted. The targets of let-7 are the Ras oncogene and *high mobility group AT-hook 2* (HMGA2). Ras is a GTPase in signal transduction that transmits signals from outside the cell to inside the cell to influence proliferation, growth, cytoskeleton organization, cell movement, and survival. HMGA2 is a nonhistone transcription factor that changes DNA conformation into an active state and is ready to be transcribed for growth, differentiation, proliferation and survival. Let-7 deletion causes Ras and HMGA2 to become uncontrolled and leads to the development of cancer (Wang and Luo, 2015).

### **CONCLUSION**

miRNAs role in post gene regulation transcription. miRNAs join with RISC and Work with method pair base with complementary mRNA so that translation stopped and induce mRNA degradation. miRNAs experience deregulation on cancer among other things, you can happen excess expression miRNAs oncogenic or deletion characteristic miRNAstumor suppressor.

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