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Review

MicroRNAs Role in Non-Communicable Diseases and Link to Multidrug Resistance, Regulation or Alteration

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Abstract: Discovery of microRNAs (miRNAs) twenty years ago, has advocated a new era of "Molecular Genetics". About 2000 miRNAs are present, that regulate one third of the genome. MiRNAs dysregulated expression may contribute to several diseases including tumor growth. Their presence in body fluids, reflecting levels alteration in various cancers, merit circulating miRNAs as the "next generation biomarkers" for early stages tumor diagnosis and/or prognosis. Herein, we performed a comprehensive literature search focusing on the origin, biosynthesis and role of miRNAs and summarized the foremost studies centering on miRs value as non-invasive biomarkers in different non-communicable diseases, including various cancer types. Moreover, during chemotherapy many miRNAs were linked to multidrug resistance, via modulating numerous biological processes and/or pathways that will be highlighted as well.

Keywords: ncRNA; miR; NCDs; onco-miR; cancer; mTOR

1. MicroRNAs History/Background

1.1. MicroRNA; the Protein Short Non-coding RNAs

The human genome reveals that the protein-coding genes can be as few as 25,000[1]. Despite the fact that the exact number of coding genes, within the human genome, is unknown, **protein non-coding genes** make up a significant portion of the human genome[2].

Human cells contain several distinguishing sequences of **non-coding RNA (ncRNA)** that could be categorized into two major classes: long ncRNA (≥ 200 nucleotides length) and short ncRNA (< 200 nucleotides). The short ncRNA group comprises different classes such as small-interfering RNAs (siRNA), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), piwi-interacting RNAs (piRNAs) and **microRNAs (miRNAs)**[3] .

1.2. MiRNAs are the Essential Gene-Expression Regulatory Molecules

MiRNAs regulate one-third of the human genome[4]. These are small single-stranded 17-25 nucleotides, recently known as essential gene-expression regulatory molecules[5].

The parent microRNAs member is **lin-4,** that has been discovered within a nematode called *Caenorhabditis Elegans*. Lin-4 was found to play a pivotal role in the transition from a larval stage into another, via suppression of *lin-4* gene, concerned with larval development[6].

MiRs are encoded either via separate transcription units within the pre-mRNA introns or via multi-cistronic clusters[7]. MiRNAs organized in clusters within the genome, are sharing the same transcriptional regulatory elements, but are expressed individually, in the event, as if they have their own promoters[8].

MiRs direct major cellular functions such as proliferation, differentiation, maturation, and metabolism[9]. Irregular expression of miRNAs may occur in a range of distinctive pathologies, with striking modifications in tumor tissues[9]. Profiling of miRNAs has contributed to the molecular classification of tumors. The presence of miRNAs in body fluids as urine, serum or plasma, CSF, and tears, permitted

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non-invasive identification of various cancer types[10],[11],[12],[13] considered as beneficial potential liquid biopsy.

2. Review Aims

2.1. In Part I, the review aims to briefly discuss ***"miRs biosynthetic pathways and down-stream effects upon binding target mRNA"***.

2.2. In Part II, the review aims to highlight ***"the utility of circulating miRNAs as biomarkers for non-communicable diseases (NCDs) and a brief about their role in cancer growth or resistance to treatment"***.

3. Review Methodology

An online search in the medical databases PUBMED and NCBI for the following terms: ("Circulating miRNA") AND ("Health and diseases regulation of gene expression") AND ("Role in Carcinogenesis") AND ("Epigenetics") AND ("Future promising biomarkers") was done on September, 2020, with publication date limit since 2015. Priority was given to papers with higher empirical evidence methodology, including clinical guidelines, meta-analysis, randomized clinical studies, systematic review, original papers, and narrative reviews.

Part I.

4. MiRNAs Biogeny

MiRNAs biogenesis include various coordinated steps and specific cellular mechanisms[8]. Biogenesis of miRNA starts with post-transcriptional or co-transcriptional preparation of RNA polymerase II-III transcripts. Around 50% of the miRNAs recently identified are intragenic and are typically regulated from introns and some protein-coding gene exons. The remaining ones are intergenic, freely transcribed and guided according to their own promoters from a host gene[14]. MiRNAs could be translated as a single long transcript, named **clusters**[15]. Moreover, miRNAs biogenesis is categorized as either canonical or non-canonical.

4.1. Canonical miRNAs Biogeny Pathway

This is the main route by which miRNAs are developed, as shown in Figure (1). In this process, primary-miRNAs (pri-miRNAs) are transcribed from their genes by RNA polymerase II. Which is then handled by a microprocessor complex composed of DiGeorge Syndrome Critical Region 8 (DGCR8); an RNA-binding protein, Drosha, a Class 2 ribonuclease III enzyme into precursor-miRNAs (pre-miRNAs)[16]. In this process, DGCR8 identifies an N6-methyl adenylated GGAC and a different motif within the pri-miRNA[16], while Drosha begins processing inside the nucleus by cutting the stem-loop precursor[17].

For most of the double stranded RNAs (dsRNAs) which are involved in small-RNA production routes, pre-miRNA seems to be a **signature motif**. This signature is recognized by the Exportin-5 protein; that facilitates the release of pre-miRNAs to the cytoplasm, through nuclear pores, depending on a GTP-GDP gradient[17]. Exported pre-miRNA is transferred to another RNase-III enzyme in the cytoplasm, called Dicer. Dicer, the cytoplasmic RNase-III enzyme, cuts the pre-miRNA to a miRNA duplex, which is un-winded afterwards giving the **"Fully Developed Functional miRNA"** molecule.

In an ATP-dependent manner, the two strands defined from the resultant miRNA duplex, might be stacked into the protein family Argonaute (AGO) known as AGO1-4[18]. After miRNA duplex formation, one strand of the miRNA associates with an RNA-induced silencing complex (RISC) forming the "regulatory miRNA-RISC complex". The choice of strands 5p or 3p is dependent on the thermodynamic stability at the 5' untranslated regions (UTRs) at the 1-position of the nucleotide[19]. The unoccupied strand known as the

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passenger strand is loosened by different components from the loaded strand, named the guide or leading strand, depending on complementarity[6].

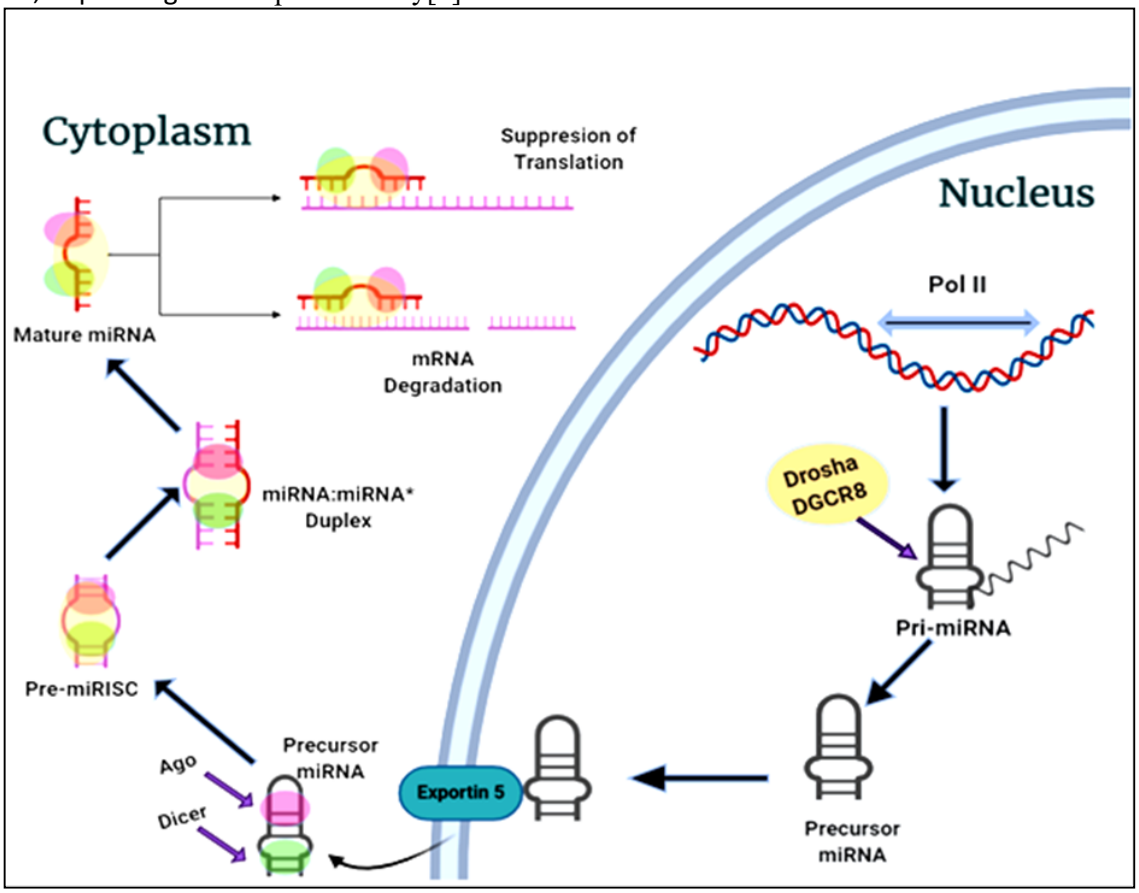

Figure 1: Canonical miRNAs Biogeny Pathway

[It is the primary route by which miRNAs are produced. In the nucleus, the gene is transcribed to generate primary miRNA (pri-miRNA) that is cleaved producing precursor miRNA (pre-miRNA), which is then exported to the cytoplasm to be broken, resulting in miRNA duplex. miRNA duplex links to RISC complex resulting in miRNA duplex unwinding to create a mature miRNA. Every mature miRNA binds to its target mRNA, resulting in silencing by cleavage, de-adenylation or repressing translation.]

4.2. Non-Canonical miRNAs Biogenic Pathway

Several non-canonical pathways have been illustrated to date, primarily Drosha/DGCR8-independent and dicer-independent pathways[6].

4.2.1. Drosha/DGCR8-Independent Non-Canonical MiRNAs Pathway

This pathway joins mRNA introns and their own transients to “mirtrons transcripts”. Drosha/DGCR8 is skipped at that stage of processing and these transcripts are, again, carried by the protein Exportin-1 to the cytoplasm[17].

4.2.2. Dicer-Independent miRNAs Biogenic Pathway

mRNAs could be dealt by Drosha/DGCR8 to form short heterogeneous RNA (shRNA). Since these transcripts are not lengthy to serve as dicer substrates, AGO2 protein leads in their cytoplasmic developmental steps[20], as previously mentioned.

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5. MiRNAs-Target Binding

Via complementarity between unique sequences, which are 2-7 bases, from the 5' end of the miRNA and certain target mRNA sequences, recognized as "**miRNA Response Elements"** (MREs), the developed miRNA attaches to its target[21].

5.2. MiRNA-Target Gene mRNA-Binding Types

5.2.1. Ideal Binding where complete complementarity occurs when miRNA binds its target ORF resulting in an **"RNA Decay"** or

5.2.2. Imperfect Binding resulting in **"Post-Transcriptional Silencing"** via mRNA de-stabilization, de-capping, de-adenylation and translational repression[6],[22].

It is worthy to mention the fundamental multifaced aspect of miRNAs target binding, is that their suppressive role is not limited to one-mRNA, highlighting the "**One-mRNA Paradigm**" in which multiple mRNA targets can be achieved by one microRNA and multiple microRNAs can hit one mRNA[23].

5.3. MiRNA-Target Gene(s) mRNA Silencing Mode(s)

Depending on the degree of MREs complementarity, the target gene(s) mRNA silencing strategies, by miRNAs, could be attained either via target gene mRNA degradation or target gene mRNA translation repression.

5.3.1. Target mRNA Decay

MiRNA-induced silencing complex (miRISC) AGO proteins bind to the GW182 (a protein-containing glycine-tryptophan repeat) to enroll the "de-adenylase complex" and promote de-adenylation of the target gene mRNA poly(A) tail. With the aid of the catalytic de-capping protein-2 (DCP2), after de-adenylation, and in the presence of an additional de-capping activators, miRISC de-caps the de-adenylated gene mRNAs. In the presence of an enhancer of de-capping 4 (EDC4), DCP1 and additional de-capping cofactors, the decay of the target mRNA is aided by the cytoplasmic 5' to 3' exonuclease1 (Xrn1p)[24]

5.3.2. Target mRNA Translation Repression

miRNA-mediated target mRNA translational repression can occur before and after translational initiation step, through several mechanisms.

5.3.2.1. miRISC ties to the target mRNA at that point AGO protein interacts with the GW182. This interaction promotes the relocation of poly(A) binding protein from the 3' poly(A)-tail and blocks its binding to the eukaryotic initiation factor 4 complex (eIF4G), interfering with the "translation-initiation step"[25].

5.3.2.2. Repressing cap-structure recognition by eIF4F complex where the AGO protein separates the eIF4A from the 5' cap binding complex of the target mRNA and therefore, the ribosomal subunit will not be recruited or attached to the mRNA for translation initiation[25].

5.3.2.3. miRNA can **repress protein synthesis** after target mRNA translation initiation.

5.3.2.4. Additionally, miRISC could interferes with the targeted mRNA **elongation components**[25].

5.3.2.5. Finally, to ensure no escape from miR silencing effect, if the target mRNA was translated, miRISC could recruit **proteases** resulting in degradation of the nascent polypeptide chains[25].

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5.4. MiRNA-Target Gene(s) Activation Mode

Activated targeted mRNA expression could be triggered by miRNAs[6], via AGO2 protein and fragile-x-mental retardation related protein-1, rather than GW182. This is achieved via MiR attachment on the target promoter, to induce RNA-Polymerase II recruitment followed by transcription activation[26].
Either "MiR-target gene(s) binding" resulted in an expression silencing or activation, these effects have been witnessed and recorded by researchers to be associated with various disease(s), that will be discussed in the current review Part II.

Part II.

6. MiRNAs Expression Alterations in Non-Communicable Diseases

6.2. MiRNAs Relation to Glucose Homeostasis

MiRNAs Effect on Adipogenesis, Metabolic Syndrome or Weight Control[27] MiRNAs may boost or inhibit mesenchymal stem cell adipogenic differentiation **(Table 1)**. MiRs establish adipocyte differentiation, through directing adipogenesis-related transcription components and signal transduction pathways[28]. This could be mediated via AKT/mTOR signaling pathway, with an effect on glucose homeostasis and adipogenesis increment, characterized by the final up-regulation of adipogenic markers[29]. On the other hand, miRNAs would repress adipogenic differentiation via adipogenic factors down-regulation, together with a decreased triacylglycerol level[30].

6.2.1. MiRNAs Relation to Type 2 Diabetes Mellitus

As listed in **Table 1**, many miRNAs are linked to ß-cells growth, insulin resistance or sensitivity, insulin production/secretion and insulin signaling, which can influence T2DM disease course[31]. Therefore, diabetes-related nephropathy or retinopathy is also affected by an altered microRNAs expression[32].

6.2.2. MiRNAs Lists in Cardiovascular Diseases

miRNAs regulate the cardiac progenitor cells differentiation and proliferation, controlling cardiac myocytes, endothelial cells, pacemaker cells, as well as smooth muscle cells function. **Table 2** shows miRNAs lists dysregulated in various CVDs[33]. For example, miR-208a and miR-208b, encoded within alpha and beta-cardiac muscle myosin heavy chain genes, respectively, were found to be elevated in patients with acute myocardial infarction (AMI). **Liu and his co-workers**[34] demonstrated a significant predictive value for miR-208, miR-1 and miR-499 in AMI, higher than the traditional cardiac biomarkers, namely, TnT and CPK-MB.

6.3. MiRNAs List in Cerebrovascular Diseases

miRNAs are essential to the nervous system's improvement, with few miRNAs having function in developing ischemic cerebrovascular disorders incapacity[35]. Many miRNAs have been associated with post-stroke brain edema and post-stroke cell death, namely, apoptosis.[36]As listed in **Table 3.**

6.4. MiRNAs in the Oncology field

6.4.1. Onco-miR or Tumor Suppressor miR; a Coin with Two Faces

Being a multifactorial player, miRNA in the oncology field represents a coin with two faces, either oncogenic or tumor suppressor[37], as listed in **Table 4**. miRNAs that can hit/suppress various mediators of the oncogenic signaling pathways, is known as a tumor suppressor mediator[38]·[39]·[40].
On the contrary, the miRNA that aims the cell-cycle checkpoint proteins or the fundamental tumor suppressor proteins, is nominated the oncogenic miRNA or an onco-miR[41].

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Table 1: MiRNAs List in relation to Glucose Homeostasis; Adipogenesis, Metabolic Syndrome, and Type 2 D.M

Metabolic Disease	miRNAs Effect	miRNAs List
Obesity & Metabolic Syndrome	Adipogenesis promoting	miR-26b[42], miR-103[43], miR-146b, miR-148a[44], miR-199a, miR-181, miR-320[28]
	Anti-adipogenic	miR-33b, miR-93[45], miR-125a, mirR-193a/b[46], miR-194, miR-363, miR-709[27]
Type 2 D.M	ß-cells development	miR-197-3p, miR-9-5p, miR-9- 3p, miR-99a-3p, miR-124a, miR-135a, miR-138, miR-149, miR-342-3p, miR-375, miR-106b, miR-222[47],[48],[49],[50],[51],[52],[53]
	Insulin sensitivity/resistance	miR-31, miR-127, miR-302c3p, miR-373, miR-518b, miR-520c-3p, miR-200, miR-7[54],[55],[56],[57],[51]
	Insulin production/secretion	miR-29, miR-221, miR-222, miR-103, miR-107, miR-223[58] miR-320, miR-126, miR-103, miR-107[59],[31] Let-7 family[60] miR-375, miR-9, miR-7, miR-124a, miR-96, miR-124, miR-184, miR-29a[47] ,[51]
	Insulin signaling	miR-7, miR-1, miR-133a/b miR-206, miR-128a, miR-330, miR-223[61],[62],[63] miR-144

Table 2: MiRNAs Lists associated with different Cardiovascular Diseases

Cardiovascular Disease(s)	miRNAs List
Acute Myocardial Infarction	miR-208a/b, miR-1, miR-133a/b, miR-499[34], miR-328, miR-134, miR-1291, miR-663b, miR-22[64], miR-126[65]
Heart Failure	miR-423-5p, miR-22, miR-320a, miR-92b[33], miR-21[66]
Atrial Fibrillation	miR-133b, miR-328[20], miR-499[67], miR-126[68]
Hypertension	miR-34a, miR-21[69], miR-23b, miR-191, miR-451, miR-126-3p, miR-26a-5p, miR-107[70]

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Table 3: MiRNAs List in some Cerebrovascular Diseases

Cerebrovascular Disease(s)	miRNA Regulatory Effect	miRNAs List
Stroke	Up regulation	miR-125b-2, miR-422a, miR-488, miR-627[71], miR-290[72], miR-124, miR-27a, miR-10a, miR-182, miR-200b[73], miR-298, miR-106b-5P, miR-4306[74]
	Down regulation	let-7f, miR-126, miR-1259, miR-142-3p, miR-15b, miR-186, miR-519e, miR-768-5p[35], miR-320e, miR-320d[35]
Alzheimer's	Up regulation	miR-146a[75], miR-361-5p, miR-30e-5p, miR-93-5p, miR-15a-5p, miR-143-3p, miR-106b-5p, miR-101-3p, miR-424-5p, miR-106a-5p, miR-18b-5p, miR-3065-5p, miR-20a-5p, miR-582-5p[76]
	Down regulation	miR-31, miR-93, miR-143, miR-146a[75], miR-1306-5p, miR-342-3p, miR-15b-3p[76]
Parkinson's	Up regulation	miR-331-5p[77], miR-137-3p, miR-124-3p[78], miR-30a/b-5p[79]
	Down regulation	miR-29a/c-3p, miR-19a/b-3p[80]

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Table 4: miRNAs Lists associated with Various Types of Cancer and their effects either oncogenic or tumor suppressor

Cancer Type	miRNA Role	miRNAs List
Leukemia	Oncogenic	miR-128a, miR-128b, miR-150, miR -155, miR-181b-5p, miR-423-3p, miR-486-5p, miR-92b-3p[81]
	Tumor Suppressor	miR-15a, miR-16-1[82], miR-495
Breast	Oncogenic	miR-1285[83], miR-10b, miR-373[37], miR-520c, mir-21, mir-155
	Tumor Suppressor	mir-125a/b, miR-142[84], miR-124-3p[85], miR-101, miR-204-5p[86], miR-491-5p[87], miR-491-5p[87], miR-206[88], miR-152[89], miR-142-3p[90]
Gastric	Oncogenic	miR-23a[91], miR-27a[92], miR-223[93], miR-106a[94], miR-106b-25 cluster, miR-107[95]
	Tumor Suppressor	miR-145, miR-143[96], miR-9[97], miR-34b[98], miR-124a, miR-335, miR-218, miR-484[99]
HCC	Oncogenic	miR-182-5p[100], miR-106b-3p, miR-101-3p, miR-1246[101], miR-221, miR-224
	Tumor Suppressor	miR-34a, miR-199a[102], miR-200a
Prostate	Oncogenic	miR-141 and miR-21[103], miR-125b[104]
	Tumor Suppressor	miR-145, miR-143[105]
Pancreatic	Oncogenic	miR-132, miR-212, miR-122-5p, miR-125b-5p, miR-192-5p, miR-193b-3p, miR-221-3p, miR-27b-3p[106], miR-222[66], miR-181a/b/d[107], miR-155, miR-103, miR-107
	Tumor Suppressor	miR-125b-5p[106], miR-34a, miR-96, miR-221
Ovarian	Oncogenic	miR-16, miR-939[108], miR-21, miR-27a, miR-26a/b, miR-103, miR-182, miR-223, miR-205[109], miR-206, miR-195, miR-10b, miR-7, miR-429[110]
	Tumor Suppressor	miR-145, miR125b, miR-211[111], miR-25, miR-93, miR-377, miR-432, miR-124a, miR-436, miR-302a[112]
Uterine Leiomyoma	Oncogenic	miR-15b[113]
	Tumor Suppressor	miR-29a/b/c, miR-197, miR-200c[113]
Thyroid	Oncogenic	mir-129-1, miR-146b, mir-183, mir-197 [114], miR-146b[115]
	Tumor Suppressor	miR-338-3p[116], miR-497[117]
Colorectal	Oncogenic	miR-1246, miR-1308, miR135b-5p, miR-183-5p, miR-18a-5p, miR18b-5p, hsa-miR-21-5p, miR-223-3p, miR-224- 5p, miR-503-5p[118]
	Tumor Suppressor	miR-1-3p, miR-133b, miR-143-3p, miR145-5p, miR-150-5p, miR-195-5p, miR215-5p, miR-375, miR-378-3p, miR497-5p[118]
Melanoma	Oncogenic	miR-195[119], miR-210[120]
	Tumor Suppressor	miR-193a, miR-33a[121]miR-let-7b/c
Pituitary adenoma	Oncogenic	miR-128a, miR-155, miR-516a-3p, miR-372, miR-181b-5p, miR-181d, miR-191-3p, miR-598[122]
	Tumor Suppressor	miR-34a[123], miR-3676-5p, miR-383[122]
Osteosarcoma	Oncogenic	miR-504[124], miR-149[125]
Neuroblastoma	Oncogenic	miR-181a/b[126], miR-1268, miR-1303[127], miR-1308, miR-1908, miR-198, miR-513/b-5p, miR-548h, miR-580
	Tumor Suppressor	miR-513, miR-548a/f-5p, miR-323-5p, miR-342[128], miR-639, miR-640, miR-641, miR-662, miR-34a[129], miR-16, miR-15a/b[130]
Lung non-small cell	Oncogenic	miR-25[131], miR-7, miR-34a, miR-328-3p[132], miR-499a[133]
	Tumor Suppressor	miR-451[134], miR-214
Bladder	Oncogenic	miR-222, miR-452, miR-6724-5p, miR-1185-1-3p, miR-6831-5p[135]
	Tumor Suppressor	miR-143, miR-99a-5p[136], miR-6087, miR-3960, miR-1343-5p[135]
Cervical	Oncogenic	miR-31[137], miR-19a/b, miR-145[138]miR-155[139]miR-125a[140]
	Tumor Suppressor	miR-34a[141], miR-886-5p[142]

6.4.2. MiRNAs Involvement in Carcinogenesis via mTOR Signaling

In different types of cancer, the **mechanistic target of rapamycin (mTOR)**; a conserved serine/threonine kinase enzyme involved in cell metabolism, could be hyperactive, leading to an abnormal cell proliferation

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and eventually cancer[143]. An association was observed between miRNA(s) and the mTOR pathway during cancer growth[143].

6.4.2.1. mTOR Signaling Pathway link to miRNA Biogenesis

Targeted Raptor mutation, a fundamental component of mTORC1 type, may affect increments in miRNA biogenesis[144]. On the other hand, Mdm2-dependent ubiquitination of Drosha, an RNase assigned to pri-miRNA formation to give pre-miRNA, therefore, mTOR activation widely suppresses miRNA biogenesis[144].

Few specific miRNA(s)-related to cancer are known to be regulated by mTOR signaling, as sketched in **Figure (2)**.

However, many miRNAs have been documented to target various mTOR signaling stages in different types of cancer, as shown listed in **Table 5**.

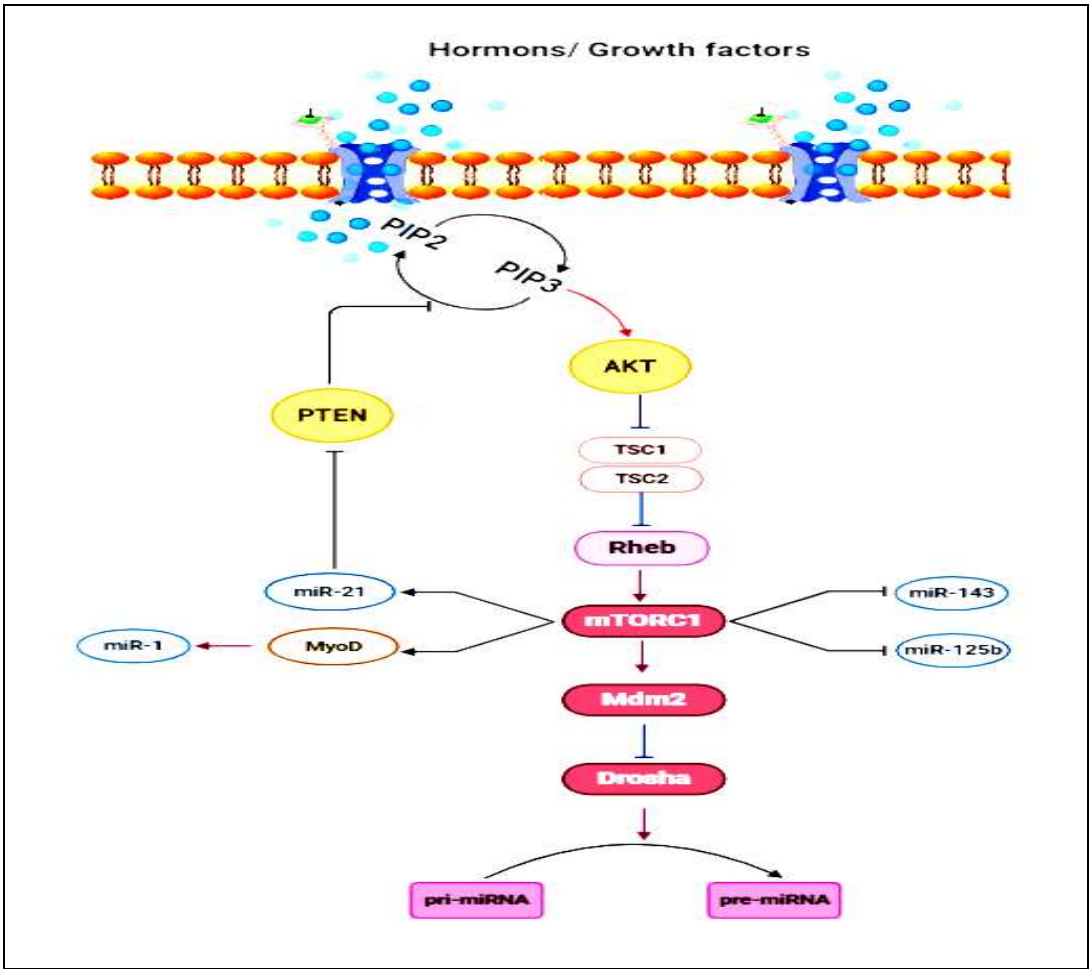

Figure 2: mTOR route Controls the Expression Levels of some miRNAs

[Through Mdm2-dependent pathway and Dorsha decaying, mTOR governs some miRNAs synthesis.]

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Table 5: miRNAs List targeting various mTOR Pathway Signals

miRNAs List	Targeted Gene(s)	Cancer Type	Effect
miR-7[145]	AKT PI_3K	HCC Adrenocortical	Proliferation Invasion
miR-99 family[146],[147],[148],[149] **(miR-99a, miR-99b, miR-100)**	mTOR AKT	Endometrial NSCLC, Cervical Breast Pancreatic HCC, Esophageal, Bladder	Proliferation, Invasion, Apoptosis, Cell Cycle, Autophagy, Tumor Formation
miR-101[143]	EZH2 mTOR	HCC, Osteosarcoma	Proliferation, Invasion, Cell Cycle
miR-122[150]	PI_3K	Breast	Proliferation
miR-149[143]	mTOR AKT	Cervical Glioma, HCC	Proliferation
miR-193a-3p/5p[151],[152],[153]	mTOR PI_3K	NSCLC	Proliferation, Migration, Epithelial Mesenchymal Transition (EMT)
miR-204[154]	mTOR	NSCLC	Metastasis
miR-155[143]	AKT S6K1 Rictor	Cervical Nasopharyngeal Breast	Autophagy
miR-214[155],[156]	AKT	Renal	Proliferation
miR-218[157],[158],[159] **miR-125a**[160]	PI_3K AKT mTOR mTOR	Colorectal OSCC Cervical HCC	Tumorigenesis Progression, Invasion, Migration Metastasis
miR-199a[161]	mTOR	Glioma, Endometrial HCC	Proliferation
miR-22[162]	mTOR	Suprarenal epithelioma	Metastasis
miR-93[163],[164],[165],[166]	PTEN	Osteosarcomas, Ovarian Breast	Proliferation, Migration, Invasion, Inhibiting Apoptosis
miR-532-5p[167]	mTOR	Gastric	Proliferation, Metastasis
miR-451[168]	mTOR AMPK	Colon	Proliferation, Migration
miR-205[169]	PTEN	NSCLC	Proliferation, Angiogenesis
miR-96[170],[171],[172]	mTOR PRAS40	Prostatic Breast Pancreatic	Proliferation, Metastasis
miR-634[173]	mTOR	Cervical	Proliferation, Metastasis, Apoptosis
miR-21	TSC	Gastric	Proliferation,

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[174],[175],[176],[177],[178],[179]	**PTEN PI3K PDCD4**	**Lymphadenoma, NSCLC, HCC, Breast Pancreatic Renal**	**Cell cycle**
miR-1271[180]	**mTOR**	**Gastric**	**Proliferation, Apoptosis**
miR-125b[181]	**mTOR**	**Sarcoma, Small cell osteosarcoma**	**Proliferation, Metastasis, Cell Cycle, Apoptosis**

6.4.3. MiRNAs and Multidrug Resistance in Cancer Therapy

Over decades, the significant clinical obstacle to successful cancer treatment is multidrug resistance (MDR), arising from ATP binding cassette (ABC) drug transporter(s) dysregulation, apoptosis or autophagy machinery surrender, redox homeostasis imbalance, as well as drug dysregulated metabolism and drug target alterations[182]. Several manuscripts addressed miRNAs role in MDR[183],[184],[185] Therefore, miRNAs might be potential targets for preventing chemotherapy MDR.
Differences in miRNAs expression pattern in drug-resistant cancer cells relative to drug-sensitive cells[182], have been reported. miRNAs list to regulate MDR by stressing on a specific cellular-signaling pathway or transporters is summarized in **Table 6**.

Table 6: miRNAs List involved in Multi Drug Resistance highlighting their regulatory function(s) and the MDR targets

Regulation of	Target	miRNAs List
MDR Transporters	**ABCB1/MDR1**	**miR-302c, miR-3664**[186], **miR-873**[187], **miR-381, miR-495, miR-223, miR-203a, miR-200c**[188], **miR-508-5p**[189]
	ABCG2/BCRP	**miR-328, miR-519, miR-520, miR-181a, miR-487a, miR-519c, miR-212**[190]
	ABCC1/MRP1	**miR-326, miR-1291, miR-508-5p**[191]
	p53	**miR-125a/b, miR-140**[192], **miR-122, miR-34**
	CDK6	**miR-34a, miR-139-5p**[193], **miR-143**[194], **miR-503, miR-1271**
	BCL2	**miR-15b, miR-16, miR-21, miR-497, miR-200bc/429, miR-1915, miR-214, miR-195**[195], **miR-205**
	BCL-XL	**miR-574-3p**
	MCL-1	**miR-101**[196]
	BIM	**miR-494**
	BAX	**miR-365**
	Caspase-3	**miR-30 b/c, miR-21**
	PTEN	**miR-21, miR-22, miR-221, miR-214, miR-19a/b, miRNA-17-5p, miR-222**[197]

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Autophagy Induction	**Beclin-1&ATG5**	**miR-30a, miR-30d/e, miR-155, miR-15a**[198]**, miR-16**[199]**, miR-200b**[191]**, miR-181a**[200]
Anti-cancer Drug Metabolism Modulation	**CYP1B1**	**miR-27b**[201]
	CYP1A1	**miR-892a, miR-130b**[202]
	CYP2J2	**let-7b**[182]
	CYP3A4	**miR-148a, miR-27b**
Drug Targets Modulation[182]	**TS enzyme**	**miR-192, miR-215**
	DPD enzyme	**miR-27a, miR-27b, miR-134, miR-582-5p**
	RRM2	**miR-211, let-7**
	MMR proteins	**miR-21, miR-155**
	BRCA1	**miR-182, miR-9, miR-218**[203]**, miR-638**[204]
GSH & GSH-dependent Enzymes	**GSH**	**miRNA-27a**[182]
	GST	**miR-513a-3p, miR-133b**[205]

7. Conclusion

7.1. One abundant class of ncRNAs is miRs. MiRs are involved in the pathogenesis as well as detection of various NCDs, including different cancer types. Moreover, miRNAs are linked to mTOR signaling pathway, a fundamental pathway of MDR and/or carcinogenesis. Current evidence indicates that in most diseases, including the NCDs, miRNAs and mTOR binding do happen.

7.2. Recommendations

Being ideal biomarkers for predicting chemotherapy response, miRs would be possible goals for future drug design to solve MDR. Additionally, combining miRNAs detection together with the mTOR signaling route components, being related to SNPs, would draw the complete picture concerning miRNAs as viable targets for evaluating and prognosticating NCDs.

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List of abbreviations

ABCB1	ATP Binding Cassette Subfamily B Member 1	**MRE**	MiRNA response elements
ABCC1	ATP Binding Cassette Subfamily C Member 1	**MRP1**	Multidrug resistance-associated protein 1
ABCG	ATP binding cassette super-family G member	**mTOR**	Mechanistic target of rapamycin
AGO	Argonaute	**NCDs**	Non communicable diseases
AMI	Acute myocardial infarction	**ncRNAs**	Noncoding RNAs
AMPK	Adenosine-5-monophosphate-activated protein kinase	**NSCLC**	Non small-cell lung carcinoma
ATG5	Autophagy related 5	**ORF**	Open reading frame
BCL-XL	B-cell lymphoma-extra large	**OncoomiR**	Oncogenic miRNA

BCL2	B-cell lymphoma 2
BCRP	Breast cancer resistant protein
CDK6	Cyclin-dependent kinase 6
CRC	Colorectal cancer
CYP	Cytochrome P450
CVD	Cardiovascular diseases
DCP	De-capping protein
DGCR8	Drosha-DiGeorge syndrome-critical region gene 8
DPD	Dihydropyrimidine dehydrogenase
dsRNA	Double stranded RNAs
EDC4	Enhancer of de-capping 4
eIF4G	Eukaryotic initiation factor 4
ERK	Extracellular signal-regulated kinase
GSH	Glutathione
GST	Glutathione S-transferases
HCC	Hepatocellular carcinoma
MAPK	Mitogen-activated protein kinase
MDR	Multidrug resistance
miRNA	MicroRNA
PD	Parkinson's Disease
PDCD4	Proapoptotic factors programmed cell death 4
PI3K	Phosphoinositide 3- kinase
piRNA	Piwi-interacting RNAs
PPARγ	Peroxisome Proliferator-activated Receptor γ
Pre-miRNAs	Precursor-miRNAs
Pri-miRNAs	Primary miRNAs
PTEN	Phosphatase and tensin homolog
Rictor	Rapamycin-insensitive companion of mTOR
RISCs	RNA-induced silencing complex
S6K1	Ribosomal protein S6 kinase beta 1
shRNAs	Short heterogenous RNAs
siRNA	Small interfering RNA
snoRNAs	Small nucleolar RNAs
snRNAs	Small nuclear RNAs
TS	Thymidylate synthase
UTR	Untranslated Region

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