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Review Article

Versatile role of miR-24/24-1*/24-2* expression in cancer and other human diseases

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Abstract: MiRNAs (miRs) have been proven to be well-validated therapeutic targets. Emerging evidence has demonstrated that intricate, intrinsic and paradoxical functions of miRs are context-dependent because of their multiple upstream regulators, broad spectrum of downstream molecular targets and distinct expression in various tissues, organs and disease states. Targeted therapy has become an emerging field of research. One key for the development of successful miR-based/targeted therapy is to acquire integrated knowledge of its regulatory network and its association with disease phenotypes to identify critical nodes of the underlying pathogenesis. Herein, we systematically summarized the comprehensive role of miR-24-3p (miR-24), along with its passenger strands miR-24-1-5p* (miR-24-1) and miR-24-2-5p* (miR-24-2), emphasizing their microenvironment, intracellular targets, and associated gene networks and regulatory phenotypes in 18 different cancer types and 13 types of other disorders. MiR-24 targets and regulates numerous genes in various cancer types and enhances the expression of several oncogenes (e.g., cMyc, BCL2 and HIF1), which are challenging in terms of druggability. In contrast, several tumor suppressor proteins (p21 and p53) have been reported to be downregulated by miR-24. MiR-24 also regulates the cell cycle and is associated with numerous cancer hallmarks such as apoptosis, proliferation, metastasis, invasion, angiogenesis, autophagy, drug resistance and other diseases pathogenesis. Overall, miR-24 plays an emerging role in the diagnosis, prognosis and pathobiology of various diseases. MiR-24 is a potential target for targeted therapy in the era of precision medicine, which expands the landscape of targetable macromolecules, including undruggable proteins.

Keywords: MiR-24/24-1*/24-2*, regulatory role in cancer and other diseases, target genes and regulatory networks, therapeutic target

MiR biogenesis

MiRs are small non-coding RNAs (ncRNAs) of around ~20-24 nt in length and function as gene regulators at the post-transcriptional level targeting mRNAs and/or affecting their translation. The first miR discovered was *lin-4* in 1993 in Caenorhabditis elegans [1]. To date, 1917 miR precursors and 2656 mature miRs have been identified in humans according to the miRBase database (http://www.mirbase.org/) [2]. The function of each miR varies considerably under different cellular circumstances [3]. MiRs are transcribed from their assigned DNA (deoxyribonucleic acid) sequences to primary miRs (pre-miRs) and further processed into precursor miRs (pre-miRs) followed by mature miRs (**Figure 1**). MiRs are synthesized via canonical and non-canonical pathways [4]. In the canonical pathway, pri-miRs are transcribed from designated genes and further processed into pre-miRs using a complex made of RNA binding protein DGCR8 (complex involving DiGeorge Syndrome Critical Region 8) and Drosha (ribonuclease III enzyme), which is famously known as “microprocessor complex” [5]. DGCR8 binds to the N6-methylated GGAC and other motifs within pri-miR, whereas Drosha mediates cleavage of the pri-miR, forming a 2nt 3’-overhang on pre-miR [4]. The generated pre-miRs are then exported to the cytoplasm by a protein complex named XPO5 (exportin 5)/RanGTPase and thereby processed using Dicer (RNase III endonuclease) to produce mature miR [6]. Various groups of common proteins [Dicer, Drosha exportin-5, and AGO-2 (Argonaute2)] were used in both pathways. Generally, non-canonical miR-biogenesis

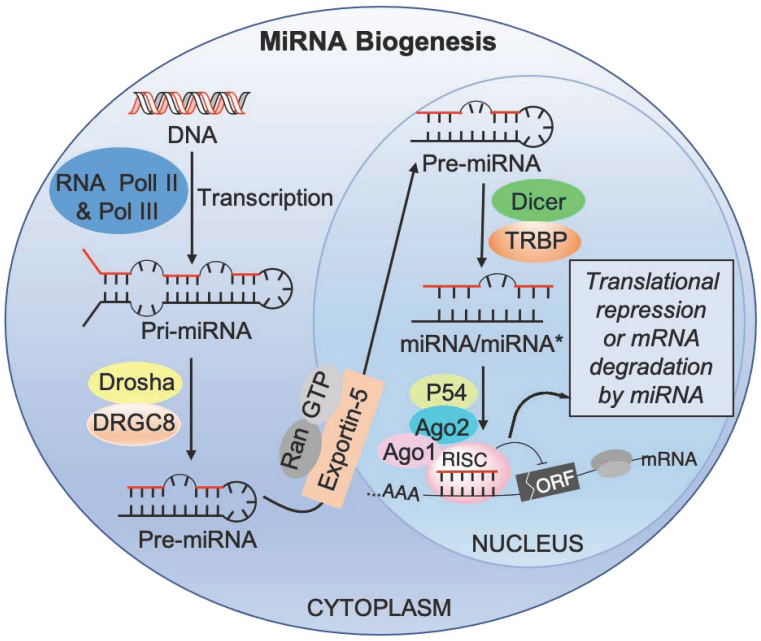

Figure 1. Schematic representation of the miR biogenesis.

can be considered a Dicer-independent and DGCR8/Drosha-independent pathway [4]. As per the majority of studies, miRs bind to a specific sequence at the 3'-untranslated region (3'-UTR) of the target mRNAs, named as seed sequences. It induces translational suppression along with deadenylation and decapping of mRNA [7] by forming the miR-induced silencing complex (miRISC) with the guide strand and AGO protein. The target specificity of miRISC is mediated by interaction with the target mRNA's complementary sequences, also known as miR response elements (MREs). The degree of complementarity is a determining factor for AGO2-dependent slicing such as miRISC-mediated translational inhibition and decay of target mRNA. The complete complementarity of the "miR:MRE" interaction activates the endonuclease activity of AGO2 and targets the cleavage of mRNA (**Figure 1**) [7].

MiR-24 clusters

MiR-24 is encoded by miR-23 and miR-27 in two different gene clusters (**Figure 2**), miR-23b-27b-24-1 and miR-23a-27a-24-2 within the intronic region of chromosome 9 (Chr9) and intergenic region of chromosome 19 (Chr19), respectively. The primary transcript of the miR-23a-27a-24-2 cluster is by ~2.2 kb long [8]. The promoter of cluster miR-23a-27a-24-2 lacks both common and less common promoter elements such as the initiator element, downstream promoter element (DPE), TFIIB recognition element (BRE), TATA box, MED-1 (multiple start site element downstream), and downstream core element (DCE). The miR-23a-27a-24-2 promoter is unique from the promoters of RNA pol II transcribed snRNA genes by lacking the proximal sequence element (PSE) [9]. Interestingly, after the primary transcript of the miR cluster is made, not all three miRs need to be formed proportionally. In HEK293T cells, overexpression of miR-23a-27a-24-2 cluster enhanced the expression of miR-27a and miR-24-2, but the expression of miR-23a remained unchanged [10]. MiR-24 is transcribed by polymerase II/polymerase III to produce a pri-miR product, which is characterized by a stem-loop structure with extensions of single strands at both ends [8, 11]. A large ductile terminal loop (≥ 10 bp) of pre-miR can be used to process 5'- and 3'-single-stranded RNA overhangs and effectively synthesizes functional miR using a microprocessor complex [12]. Runx1 and AML1-ETO occupy the miR-24a-23a-27-2 locus in chr19 and reciprocally controls miR-24 transcription [13].

A single miR in any cluster has multiple upstream and downstream regulators that target numerous mRNAs and regulate different signaling pathways and cellular processes depending on the cell context. MiRs might be misregulated in several diseases, including cancer. In addition, miRs can be used as biomarkers in clinical settings because of their extreme stability and ease of detection. Bioinformatics analysis using miRDB (http://mirdb.org/) revealed 959 predicted targets of miR-24. Similarly, as per TargetScan v7.2 (http://www.targetscan.org), 761 predicted transcripts have conserved sites for the miR-24 target. To date, it has been predominantly summarized regarding the cooperative effect of three miRs in miR-23a-27a-24-2 clusters on human diseases and cancer [14-17]. In this review, we have summarized the compre-

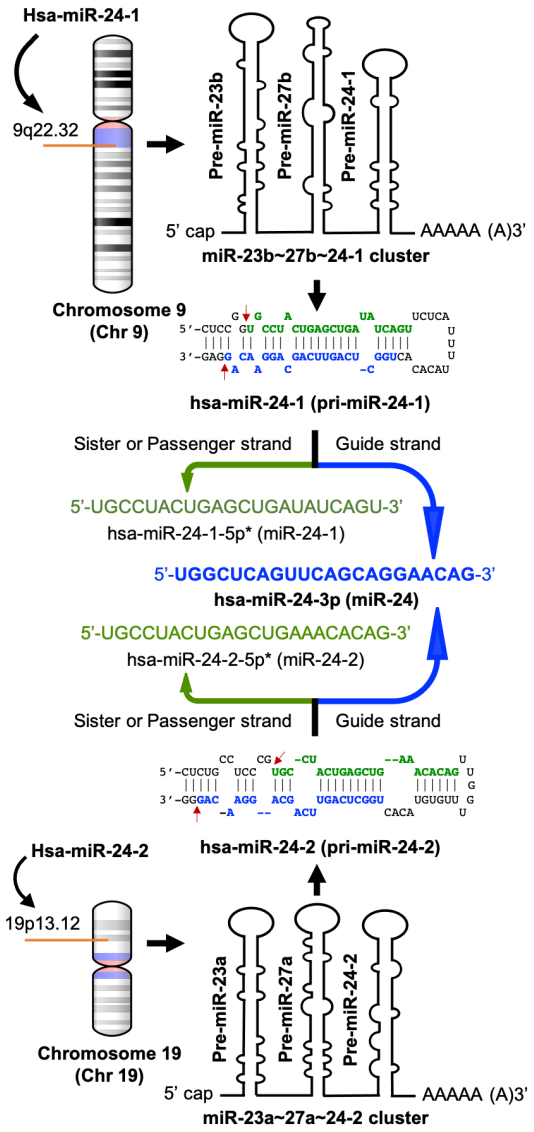

Figure 2. Alignment of two different precursors (has-miR-24-1 and has-miR-24-2) of miR-24 located (denoted by orange line) in two distant chromosomal regions (9q22.32 and 19p13.12) in human genome. Both the precursors after processed by RNase-III-type enzymes (Drosha and Dicer) formed identical mature products has-miR-24-3p (miR-24). Sequences and predicted hairpin loop structures of both hsa-miR-24-1 (pri-miR-24-1) and hsa-miR-24-2 (pri-miR-24-2) also represented into the figure. Sequences represented in blue corresponding to guide strand miR-24-3p (miR-24) sequence. Sequences of the sister or passenger or star (*) strand formed (miR-24-1 and miR-24-2) after maturation of both the precursors are represented in green. Red arrows represented the Drosha cleavage site.

hensive role of miR-24 along with miR-24-1 and miR-24-2 in different types of cancer as well as other diseases, emphasizing its significance for targeted therapy.

MiR-24 in various cancer

Similar to other miRs, miR-24 expression is deregulated in different cancers, at different stages of tumorigenesis and it has also been shown to function as a tumor suppressor (TS) or oncogenic (oncomiR) depending on the cell context. Herein, we encapsulated the association of miR-24 (**Figure 3** and **Table 1**) as well as miR-24-1 (**Figure 4** and **Table 2**) and miR-24-2 (**Figure 4** and **Table 3**) in various cancers, highlighting its roles in regulation of different biological processes, cancer phenotypes, target genes and pathways in each cancer type.

Bladder cancer (BDC)

Reviews on miRs [18, 19] in BDC have referred to miR-24 as a TS. Reduced expression of miR-24 is associated with enhanced expression of CARMA3 in BDC cells. Enhancement of miR-24 expression inhibits proliferation, arrested cell cycle and induces apoptosis. Additionally, suppression of BDC cell invasion and epithelial-to-mesenchymal transition (EMT) was observed under reduced levels of miR-24. Bioinformatics analysis and a luciferase-reporter assay proved CARMA3 as a potential target of miR-24 [20]. In contrast, another study reported [21] a higher expression of miR-24 in BDC tissues than in the adjacent non-cancerous tissue samples. In human ureter epithelium cells (HCV29), the relative mRNA expression of death effector domain-containing protein (DEDD) was higher than that in BDC cell lines (HBC, BLU87, T24 and UM-UC-3). The T24 cell line had the highest level of miR-24 and the lowest level of DEDD. Ectopic expression of miR-24 affects the proliferative and invasive characteristics of BDC cells (T24 and HBC). MiR-24 also stimulates T24 and HBC cell proliferation, significantly increases cell migration, induces apoptosis and upregulates autophagy marker LC3. A luciferase-reporter assay indicated that miR-24 promotes oncogenesis by blocking DEDD [21].

On the other hand, reduced miR-24-1 expression was mainly observed in BDC tissues and cell lines (BOY and T24), suggesting its functions as a TS [22-25]. MiR-24-1 restoration instigates apoptosis and impedes proliferation of BDC cell. Forkhead box protein M1 (FOXM1) has been reported as an immediate target of miR-24-1. Elevated expression of FOXM1 has been validated in BDC clinical samples, and FOXM1 silencing instigates apoptosis in cancer

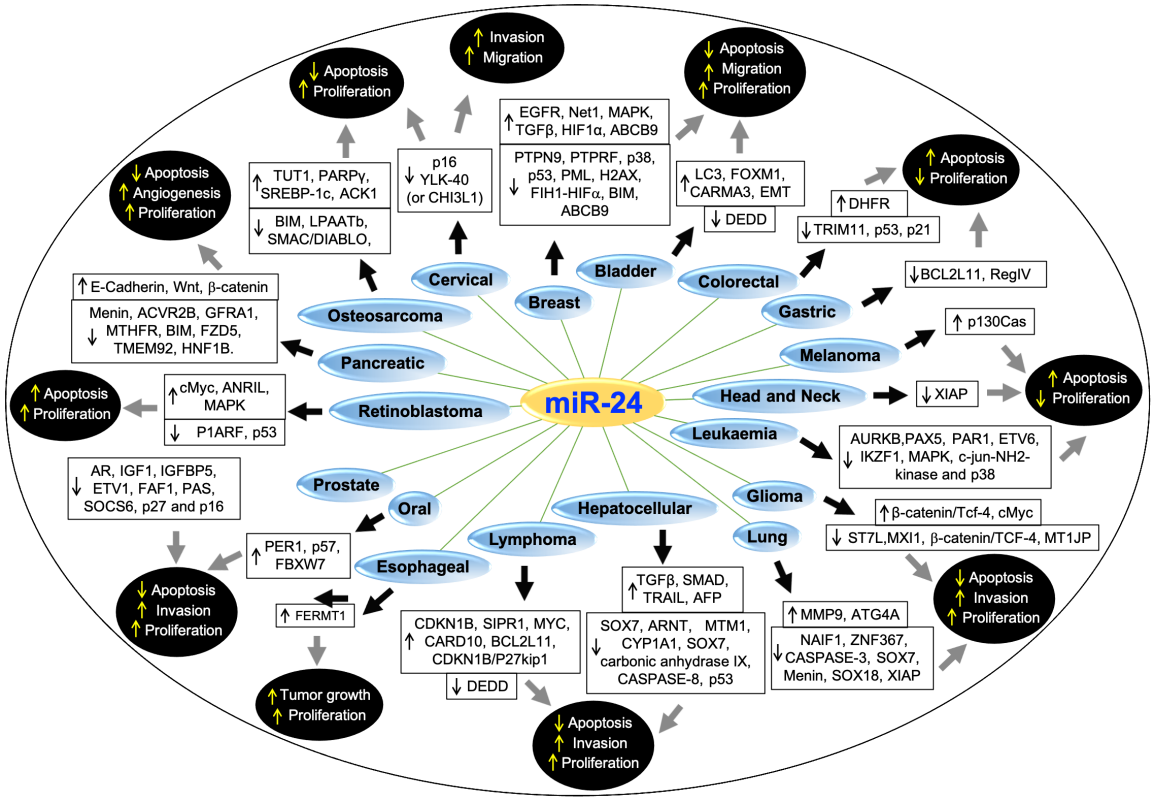

Figure 3. Schematic representation of target genes, regulatory pathways and interactive function of miR-24 in different cancer types. Black thick arrow directed from each cancer type indicates the regulatory genes. Gray thick arrow indicates the regulatory cancer phenotypes. Black thin arrow pointed upward and downward indicate the upregulation and downregulation of the corresponding gene's expression, respectively. Yellow arrow pointed upward and downward indicate the upregulation and downregulation of the corresponding phenotypes, respectively.

cells [25]. A study on urinary miRs reported that despite adverse handling conditions, miR-24 was stable within urinary cells from patients with cancer compared to controls [18, 23].

Breast cancer (BRC)

Among many miRs aberrantly expressed in BRC [26, 27], the expression of miR-24 is reported to be enhanced in BRC samples compared to that in benign breast tissues. According to genome-wide miR analysis using SOLiD sequencing, seven miRs (miR-103, -23a, -29a, -222, -23b, -24 and -25) were found to be co-upregulated in BRC tissues [28]. Several oncomiRs are overexpressed during the diagnosis of early BRC (EBRC) patients. The expression of five miRs (let-7a, miR-19a, -24, -155, and -181b) in the serum of 63 EBRC patients and 21 healthy individuals was determined after surgical resection and after chemo and/or radiotherapy. In the case of high-risk patients, miR-155, miR-19a, miR-181b, and miR-24 in serum were notably enriched compared to the low-risk group, whereas the expression of miR-19a decreased significantly after the therapy [27]. Another follow-up study of EBRC patients (*N* = 133) by the same group reported miR-155 and miR-24 as oncomiR and its association with EBRC relapse [29]. All miRs in the miR-23-27-24 clusters are upregulated in BRC and act as oncogenes by simultaneously targeting HIC1. HIC1 and miR-23-27-24 regulate each other, creating a double-negative feedback loop [30]. The overexpression of miR-24 and miR-378 was examined in BRC patients (N = 101) and controls (N = 40) [31]. Patients with increased levels of miR-24 in both plasma and BRC tissues showed increased metastasis and low survival rate compared to patients with lower expression of mir-24 in the TCGA cohort [32]. Single nucleotide polymorphisms (SNPs) regulate the size of the pre-miR terminal loop. Genetic mutations in the miR-23a-24-2-27a

Table 1. Deregulated expression of miR-24 and its regulatory genes in various cancers

Cancer	Up/Down (MiR-24)	Role (MiR-24)	Regulatory genes/pathways		Regulatory biological functions	Tissue/Sample type
			Upregulated	Downregulated		
Bladder	Down	TS	CARMA3, EMT	-	Proliferation, apoptosis, cell cycle	T24, UMUC-3, J82, 5637 SV-HUC-1
	Up	OncomiR	LC3, FOXM1	DEDD	Proliferation, apoptosis, migration	T24, UM-UC-3, HBC, BLU87, HCV29, patient
Breast	Up	OncomiR	EGFR, Net1, MAPK, TGFβ, HIF1α	PTPN9, PTPRF, p38, p53, PML, H2AX, BIM, FIH1-HIFα	Metastasis, invasion, tumor growth, proliferation, apoptosis, drug resistance	Patient, MCF-7, MDA-MB-231, BALB/c, T47D, CAMA, HBL-100, MCF7, MDA-MB-468, BT-549, BCSC
	Down	OncomiR	ABCB9	-	Drug transportation, anti-tumor effect, and paclitaxel resistance	paclitaxel-resistant (PR) breast cancer patients, MCF-7/PR cell
Colorectal	Down	TS	DHFR	TRIM11, p53, p21	Proliferation, apoptosis	Patient, HCT116, HT29, SW480, SW620, DLD-1, LoVo, HCT8, RKO, CaCo2
	Up	-	-	Paxillin, IFN-γ and TNF-α	-	Patient, NK-cells
Cervical	Up	-	-	$p16^{INK4a}$, YKL-40 or (CHI3L1 or hCGP-39)	Proliferation, migration, invasion	CaSki, SiHa, ME-180, HeLa, WI-38, Patient
Esophageal	Up & Down	TS	FERMT1	-	Proliferation, radiation resistance	Patient
Glioma	Up	OncomiR	-	ST7L, MXI1, β-catenin/TCF-4, MT1JP	Proliferation, invasion, apoptosis	U87, LN229, SNB19, U251 and LN308, SHG-44, U251, patient
Gastric	Up	-	-	BCL2L11, RegIV	Metastasis	AGS cell, patient
Head and Neck	Up	OncomiR	-	-	Metastasis	Patient sample, HPV positive tonsillar tumor samples
	Down	TS	-	XIAP	Colony formation, tumor growth and apoptosis, radioresistance	LSCC cell line, Patient, CNE-1, CNE-2, CNE-2R, HONE-1
Hepatocellular	Up	OncomiR	TGFβ, SMAD, TRAIL, AFP	SOX7, EMT, metallothionein 1M (MTM1), ARNT, CYP1A1, carbonic anhydrase IX, Caspase-8, p53	Metastasis, apoptosis, cell viability, invasion	Patient, A549, NCI-H358, NCI-H1299, H460, HepG2R, Rel-7402R, HuH-7, HepG2
	Down	-	-	-	-	Cirrhotic liver tissues, HA22T/VGH, patient
Leukaemia	Up	OncomiR	-	AURKB, PAX5, PAR1, ETV6, IKZF1, MAPK, c-jun-NH2-kinase and p38 kinases	Cell growth, proliferation, granulocytic differentiation, cell cycle, apoptosis	Patient, 697, KASUMI-2, MHH-CALL-3 TCF3, HEP-G2
Lung	Up	OncomiR	MMP9, ATG4A	NAIF1, ZNF367, CASPASE-3, SOX7, Menin, SOX18, XIAP	Invasion, autophagy,	Patient, A549, NCI-H358, NCI-H1299, H460, NCI-H1703, NCI-H522, A549
Lymphoma	Up		CDKN1B, SIPR1, CARD10, BCL2L11, CDKN1B/$p27^{kip1}$, cMyc	DEDD	Migration, invasion, cell growth	L136, L4, L1236, L428, KM-H2, patient
Melanoma	Down	TS	p130Cas	-	Migration, invasion, and proliferation	B16F10
Oral	Up	-	-	PER1, p57, FBXW7	Tumor progression, proliferation, migration, invasion	OC3, OECM-1, SAS, patient, 293T, NHOKs, UM1, UM2, Cal27, SCC1, SCC15, SCC25
Osteosarcoma	Up	-	-	BIM, SMAC/DIABLO	Doxorubicin-resistance, apoptosis	Patient, MG-63, HOS
	Down	-	TUT1, PARPγ, SREBP-1c, ACK1	LPAATb	Metastasis	Patient, U2OS
Pancreatic	Up	-	E-cadherin, Wnt, β-catenin	Menin, ACVR2B, GFRA1, MTHFR, BIM, FZD5, TMEM92, HNF1B	Cell cycle, cell viability, proliferation, tumor growth, angiogenesis	Panc-1, MIA PaCa-2, BxPC-3, Hs766T, ASPC-1, Capan-1, Capan-2, Panc3.27, HPAF-II, PL45, lox-5, patient
Prostate	Up	-	-	AR, IGF1, IGFBP5, ETV1, FAF1, PAS, SOCS6, p27 and p16	Proliferation, migration, invasion, apoptosis, cell growth, clonogenic potential, cell cycle	PC3, DU145, LNCaPFG, patient
Retinoblastoma	Up	-	cMyc, ANRIL, MAPK	P1ARF, p53	Cell growth, viability, migration, invasion	RB 247, 381, 1021, WERI-Rb1, Y79, B247, RB381

AL: Acute leukemia; AML: Acute myeloid leukemia.

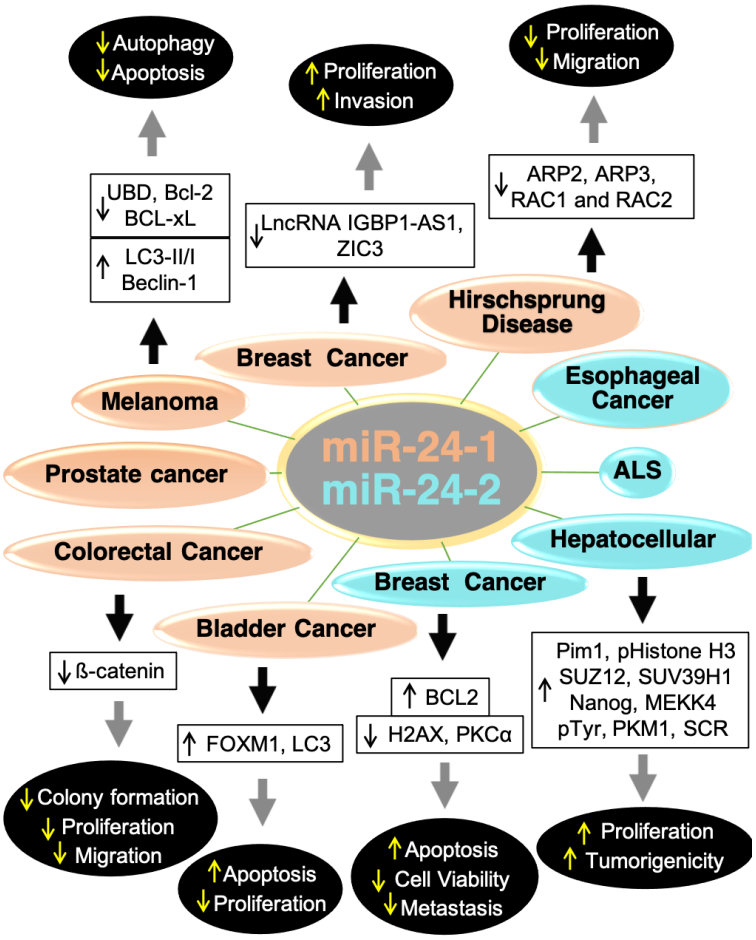

Figure 4. Schematic representation of target genes, regulatory pathways and interactive functions of miR-24-1 and miR-24-2 in various cancers and other diseases. Black thick arrow directed the regulatory genes. Gray thick arrow indicates the regulatory phenotypes and biological functions. Black thin arrow pointed upward and downward indicate the upregulation and downregulation of the corresponding gene's expression, respectively. Yellow arrow pointed upward and downward indicate the upregulation and downregulation of the corresponding phenotypes, respectively.

gene cluster of BRC patients revealed both heterozygous (A/G allele) and homozygous (G/G allele) variants in miR-27, whereas no mutations were detected in miR-23a and miR24-2 [33]. Ectopic expression of miR-24 induces migration and invasion of BRC cells. An *in vivo* study using BALB/c mice specified that miR-24 expression is required for the enhancement of tumor growth, invasion and metastasis, along with diminished overall mouse survival. MiR-24 expressing cells and tumors are associated with higher EGFR phosphorylation and reduced expression of PTPN9 (tyrosine-protein phosphatase non-receptor type 9) and PTPRF (receptor-type tyrosine-protein phosphatase F). PTPN9 and PTPRF are direct targets of miR-24 [34]. Overexpression of miR-24 promotes proliferation and inhibits apoptosis in MDA-MB-468 and MDA-MB-435 cells. The cell cycle regulatory protein $p27^{Kip}$ was identified as a direct target of miR-24, and negative regulation of $p27^{Kip}$ protein expression by miR-24 [35]. ING5, a suppressor of proliferation and invasion, was significantly downregulated in the BRC tissues. MiR-24 is a direct upstream regulator of ING5 and acts as an oncomiR. MiR-24 accelerated xenograft tumor growth in nude mice [36]. The addition of O-GlcNAc to certain serine or threonine moieties on proteins was catalyzed by OGT (O-GlcNAc transferase) and correlated with BRC cell (MDA-MB-231) invasion. OGT overexpression promoted cell invasion, whereas silencing of OGT showed the opposite effects. OGT has been recognized as a target of miR-24. OGT expression was downregulated by miR-24, followed by the suppression of cell invasion. Overexpression of OGT significantly rescued miR-24-mediated repression of invasion [37]. In addition, miR-24 is involved in the drug resistance of BRC. Post-transcriptionally, miR-24 levels decrease with long-term melatonin treatment. Melatonin-mediated downregulation of miR-24 inhibits cell migration and proliferation through hnRNPA1. MiR-24 targets several genes associated with DNA repair, simultaneously targets PML, H2AX, p38 and p53, and overcomes the effect of melatonin [38]. In MCF-7/PR human BRC cells and paclitaxel-resistant (PR) BRC patients, miR-24 was significantly downregulated. Upregulated miR-24 expression enhances the effect of paclitaxel on drug-resistant of BRC cells. The ATP binding cassette B9 (ABCB9) expression was downregulated by binding of miR-24 to its 3'-UTR, that reduced drug trans-

Table 2. Deregulated expression of miR-24-1 and its regulatory genes in cancer and other diseases

Diseases	Up/Down (MiR-24-1)	Role (MiR-24-1)	Regulatory genes/pathways		Regulatory biological functions	Tissue/Sample type
			Upregulated	Downregulaed		
Bladder Cancer	Down	TS	FOXM1 LC3		Proliferation, Apoptosis	BOY, T24, Patient
Breast Cancer	Down	oncomiR	-	lncRNA IGBP1-AS1, ZIC3	Invasion, proliferation	HCC70 and UACC-812, 76 N-F2V
Colorectal Cancer	Up	TS	-	β-catenin	Proliferation, migration and survival	colon tissue of azoxymethane/dextran sulphate sodium-induced mice, HCT-116, Caco-2
Melanoma	Down	TS	LC3-II/I, Berclin-1	UBD, BCL-xl, BCL-2	-	A375 cell line, patient
Prostate Cancer	Down	-	-	-	-	patient
Syndrome	Up in HSCR	-	-	ARP2, ARP3, RAC1 and RAC2	Migration, proliferation	293T, SHSY5Y

HSCR: Hirschsprung disease.

Table 3. Deregulated expression of miR-24-2 and its regulatory genes in cancer and other diseases

Diseases	Up/Down (miR-24-2)	Role (miR-24-2)	Regulatory genes/pathways		Regulatory biological functions	Tissue/Sample type
			Upregulaed	Downregulated		
Breast Cancer	Down	TS	H2AX, PKCα	BCL2	DNA-damage, Apoptosis, metastasis, cell cycle	MCF-7
Esophageal Cancer	Up	-	-	-	-	patient
Hepatocellular Cancer	Up	-	PIM1, SRC	PKM1	Tumorigenic, proliferation	-
ALS	Up	-	-	-	-	Rat tissue, patient samples

ALS: Amyotrophic lateral sclerosis.

portation and improved the anti-tumor effect of paclitaxel on BRC cells [39]. MiR-24 is upregulated in BRC stem cells and the expression of stem cell markers and the number of mammospheres enhanced by overexpression of miR-24. Through the regulation of BimL expression, miR-24 induces resistance to apoptosis. FIH1 is a new target of miR-24 that promotes the degradation of HIFα. MiR-24 expression was enhanced under hypoxic conditions, causing FIH1 repression and enhancement of HIF1α expression [40]. In BRC cells, ectopic expression of miR-24 in tamoxifen-resistant MCF7 augmented tamoxifen-induced cell viability inhibition, while miR-24 knockdown partly mitigated the cytotoxic effect of tamoxifen. MiR-24 targets Bim in tamoxifen-resistant MCF7 cells [41].

In both sporadic breast tumor tissues and BRC cell lines (MCF7), a negative correlation between expression of H2AX and miR-24-2 expression was observed by *in silico* analysis. In addition, the hypersensitive nature of ectopic miR-24-2 expression has been reported for DNA-damaging drugs and endures apoptotic cell death. BCL-2 was recognized as a novel target of miR-24-2 and was confirmed by a luciferase assay. By regulating various apoptotic pathways and targeting the anti-apoptotic gene BCL-2, mir-24-2 is capable of inducing apoptosis, although the study suggested that miR-24-2 is more implicit in controlling H2AX gene expression, regardless of the change in gene copy number [42]. MiR-24-2 acts as a TS in the BRC cell line MCF-7. Pre-miR-24-2 overexpression leads to the enhancement of miR-24-2 levels compared to miR-24 and decreases the expression of its mRNA target, PKCα and phorbol 12-myristate 13-acetate (PMA)-mediated *in vitro* cellular survival [43]. Manvati et al. reported that miR-24-2 negatively correlated with metastasis and validated the use of miR-24-2 in combination with the anticancer drug docetaxel to reduce cell viability in sporadic ductal BRC tissue samples [44]. The expression of lncRNA IGBP1-AS1 decreased in BRC as well as *in vitro* and *in vivo* experiments. The study confirmed that the lncRNA IGBP1-AS1/miR-24-1/ZIC3 loop is involved in breast cancer proliferation and invasion and can be regarded as a new therapeutic target [45].

Colorectal cancer (CRC)

In human CRC cell lines (HT29, HCT116, SW620, SW480, LoVo, DLD-1, RKO, HCT8, and CaCo2), silencing of E3 ubiquitin ligase TRIM11 (tripartite motif-containing protein 11) suppressed cell proliferation and induced apoptosis with increased levels of miR-24 [46]. CRC tumor samples had reduced levels of miR-24 and these patients had a poorer prognosis compared to those with high miR-24 levels. Overexpression of miR-24 in SW480 and HT29 cells suppressed CRC cell proliferation, migration and invasion [47]. Overexpression of miR-24, independent of p53 function, suppressed proliferation and G2/S cell cycle arrest in six different cell lines. MiR-24 has anti-tumorigenic properties by regulating dihydrofolate reductase (DHFR), a target of methotrexate (MTX). Polymorphism of the miR-24 target site in the 3'UTR of DHFR resulted in the functional privation of miR-24. High levels of DHFR transmit a growth advantage to immortalized cells and induce neoplastic transformation [48]. Cox regression analysis of colorectal adenocarcinomas confirmed that miR-24 overexpression was a significant indicator of poor prognosis [49]. In the plasma samples from 223 patients with colorectal related diseases [111 cancer carcinoma, 59 adenoma, 24 colorectal polyps and 29 inflammatory bowel disease (IBD)], miR-24, miR-320a and miR-423-5p levels were decreased in patients with CRC and benign lesions (polyps and adenoma) compared with IBD and healthy controls. MiR-24, miR-320a, and miR-423-5p levels in plasma have been reported as potential novel biomarkers for CRC detection, mainly in the early stages [50, 51]. Contrary to the tumor-suppressive role of miR-24 in CRC, few reports have suggested that miR-24 is responsible for its progression. MiR-24 was overexpressed in the CRC patient's NK cells compared to that in healthy volunteers. Interference of paxillin by overexpression of miR-24 significantly decreased paxillin expression, secretion of IFN-γ and TNF-α, and the NK cell's killing effect on CRC cells [52]. Under hypoxic conditions, miR-23a-27a-24 was overexpressed. Gain and loss-of-function assays, human glucose metabolism array and analyses of gene pathways confirmed that miR-23a-27a-24 cluster induced by HIF-1α concomitantly regulate glucose metabolic networks by regulating numerous metabolic pathways and by targeting multiple tricarboxylic acid cycle (TCA)-related genes [53]. MiR-24-1 is a dominant regulator of β-catenin and may render a novel therapeutic and chemopreventive strategy for β-catenin signaling-driven CRC [54].

Cervical cancer (CC)

Four miRs (MiR-21, -24, -27a, and -205) were identified as the most abundant miRs in the HPV16$^+$ CC cell line CaSki [55]. MiR-24 was also reported to suppress p16^{INK4a} protein expression but not p16^{INK4a} mRNA in human diploid fibroblasts (WI-38) and CC cells (HeLa) [56]. The recursive feature elimination technique was used to rank the miR's in the CC outcomes. Ten top-ranking miRs (miR-9, -200a, -10b, -183, -204, -24, -181a, -193b, -146b and -10a) were selected by SVM-RFE and were associated with CC survival [57]. The inflammatory glycoprotein YKL-40, known as hCGP-39 (cartilage glycoprotein-39) and CHI3L1 (chitinase-3-like protein 1), plays a vital role in angiogenesis, extracellular matrix degradation and tissue remodeling in CC using serum samples from 59 patients. The 3'-UTR of YKL-40 is suggested to be a formal target of miR-24. MiR-24 influences the regulation of YKL-40 levels and facilitates the proliferation, migration and invasion of CaSki cells [58].

Esophageal (Oesophageal) cancer (EC)

As per the qRT-PCR data of oesophagal squamous cell carcinoma (ESCC) patient's serum samples [radio-sensitive group (CR+PR, 62 patients), radio-resistant group (SD+PD, 43 patients) and 30 healthy volunteers], miR-24 level was 4.82 times higher than that in healthy groups (P<0.01), indicating that miR-24 is a potential diagnostic factor [59]. MiR-24 suppressed the expression of FERMT1 by directly binding to the 3'-UTR, thereby suppressing cell growth and enhancing the radiosensitivity of EC cells, and re-expression of FERMT1 reversed these effects *in vitro* and *in vivo* [60]. Significantly upregulated expression of miR-27a and miR-24-2 was also reported in ESCC tumor specimens compared to that in adjacent normal tissues [61].

Glioma (GL)

MiR-24 was upregulated in GL clinical specimens and cell lines (human glioblastoma cells U87, LN229, SNB19, U251 and LN308; low-grade glioma H4 cells) by qRT-PCR. Inhibition of miR-24 in GL cells prohibited proliferation, invasion and induced apoptosis. Using miRanda and miRvr, suppressor of tumorigenicity 7 protein-like (ST7L) [62] was pointed out as a candidate target of miR-24 and confirmed by luciferase-reporter assay with the 3'-UTR-ST7L, thereby reducing the activity of β-catenin/Tcf-4 transcription activity by involving ST7L targetability [63]. Overexpression of miR-24 along with miR-27a promotes cell proliferation in human GL tissue and cell lines (U87 and U251) by targeting MXI1, a TS gene that regulates cMyc. Both miRs promoted GL cell proliferation by acting on MXI1. Furthermore, the data showed that regulation of MXI1 synergistically by two clusters of miR-23a-27a-24-2 and miR-23b-27b-24-1 [64]. Transient expression of long non-coding RNA (lncRNA) MT1JP (metallothionein 1J) inhibited the invasion and proliferation of GL cells. The interaction of MT1JP with miR-24 was also revealed by a dual-luciferase assay [65]. MiR-24 was also identified as one of the top ten ranked miRs in terms of its interdependency with survival time in patients with glioblastoma multiforme using support vector regression (SVR)-based method (SVR-GBM) [66].

Gastric cancer (GC)

Investigation of miR-24 and miR-101 expression in 247 GC clinical specimens and 150 cancer-adjacent non-tumor tissues from advanced GC patients revealed significantly upregulated expression of miR-24 in GC tissues (t = 10.26, P<0.01) [67].

Hepatocellular (liver) carcinoma (HCC)

In primary HCC samples, microarray data in response to TGF-β showed variations in miR levels. In an odd case of HCC cell lines, Huh-7 and SMMC-7721 demonstrated distinct responses to TGF-β stimulation. The miR-23a-27a-24 cluster was highly expressed in TGF-β induced SMMC-7721 and primary HCC patient samples in Smad-dependent manner and involved in intrahepatic metastasis [68]. HCC related to aflatoxin B1 (AFB1) I-II tumor node metastasis stage clinical samples and cell lines, miR-24 was upregulated. High miR-24 expression leads to a poor prognosis. MiR-24 integrates with alfatoxin-B-DNA adducts and both together result in poor patient survival [69]. In HCC patient samples and cell lines (HepG2, QGY-7703, MHCC-97H, and Huh7), the expression of miR-24 was higher than that in healthy tissues. Inhibition of miR-24 resulted in reduced proliferation and invasion by targeting SOX7 [70]. MiR-24 is upregulated in tumor

recurrence in HCC following orthotopic liver transplantation. GO and KEGG pathway analyses showed that the MAPK and Wnt pathways are targets of miR-24 [71]. MiR-24 and miR-221 were upregulated in TRAIL-resistance HCC cells (TRAIL-resistant HepG2R and Bel-7402R). MiR-221 and miR-24 target Caspase 3 and Caspase 8, respectively. In HepG2R and Rel-7402R cells, CASC2 (cancer susceptibility candidate 2) and miR-24/miR-221 were correlated with AGO2. CASC2 knockdown reduced the protein levels of caspase 8, 3 and cleaved caspase 8, 3. TRAIL treatment assessed tumor cell apoptosis with the combined effect of CASC2 knockdown and miR-24/221 silencing [72]. The lncRNA cancer susceptibility candidate 2 (CASC2) was reduced in HCC cell lines (HepG2 and HuH7) and miR-24 was upregulated in HCC cell lines. Upregulation of miR-24 greatly eliminated CASC2-induced effects in both cell lines and rescued the inhibition of CASC2 on tumor growth in mice. CASC2 represses HCC cell viability and induces apoptosis by negatively regulating miR-24 and miR-24 overexpression easily overcomes the inhibitory phenotype of CASC2 [73]. MiR-24 was significantly upregulated in HCC tumor tissues, HCC cell lines (Huh7 and HepG2) and BALB/c nude mice injected with HepG2 cells. MiR-24 increased tumorigenesis and increased tumor volume in mice models by targeting TS metallothionein 1M [74]. Salvi et al. determined the expression of miRs in the human HCC cell line, HA22T/VGH. In HCC tissues and their peritumoral counterparts from biopsy, dysregulated levels of three miRs (miR-24, -27a and -21) were observed. In cirrhotic liver tissues of HCCs, miR-24 and miR-27a were markedly deregulated compared to those from non-cirrhotic liver tissues. MiR-24 and miR-27 showed a significant decrease in HCV and HBV/HCV subclasses, whereas miR-21 levels remained unchanged [75]. In contrast to this study, in inpatient samples of HCC caused by HBV-2 serum, miR-24 levels were found to be remarkably higher in clinical samples than in normal tissue samples and chronic liver disease patient samples. High levels of miR-24 have been reported in invasion, along with the overexpression of alpha-fetoprotein [76]. MiR-24 overexpression showed translational repression in HuH-7 and HepG2 cell lines by a notable reduction in ARNT at the protein level but not at the transcript level [77]. HepG2 cells treated with arsenic trioxide showed upregulated expression of miR-24, miR-29a, miR-30a and miR-210 [78, 79]. Moreover, miR-24-2 is upregulated in human liver cancers. Yang et al. reported that miR-24-2 facilitated liver cancer cell progression by activating Pim1 and suggested the miR-24-2 mediated alteration of several other genes (pHistone H3, SUZ12, SUV39H1, Nanog, MEKK4, pTyr) [80]. MiR-24-2 also facilitates *in vivo* tumorigenic and *in vitro* cell proliferation ability of human liver cancer stem cells by promoting PKM1 binding and Src activity [81].

Head and neck cancer (HNC)

Few studies have implicated miRs as oncogenic or TS in HNC [82-84]. MiR-24 expression was found to be elevated in 100 clinical specimens [85]. LSCC (laryngeal squamous cell carcinoma) is a subgroup of HNC that forms in the squamous cells of the upper digestive tract. MiR-24 was found to be downregulated in LSCC cell lines and tissues compared to human keratinocyte cell lines or adjacent normal cancer tissues. Functional analysis of LSCC cells indicated that the enhancement in the expression of miR-24 inhibited growth, colony formation, and increased apoptosis. In addition, XIAP may be a target of miR-24 and is correlated with the aggressive progression of LSCC [86]. MiR-24 was also reported to be differentially expressed in HPV-positive tonsillar tumor samples [87]. The miR-24 promoter was found to be hypermethylated in radioresistant nasopharyngeal carcinoma cell lines (HONE-1 and CNE-2R) compared to the corresponding radiosensitive nasopharyngeal carcinoma cell lines (CNE-1 and CNE-2) [88].

Oral cancer (OC)

Several miRs, along with miR-24, have the potential to be diagnostic and prognostic markers for improving care for OC [89-91]. MiR-24 was relatively upregulated in oral squamous cell carcinoma (OSCC) tissues and in the plasma levels compared to control samples. MiR-24 expression was found to be elevated in OSCC cell lines (OC3, OECM-1 and SAS) compared to normal oral keratinocytes (293T and NHOKs). MiR-24 is involved in the growth of OSCC cells and target p57 and has been concluded as a biomarker [92]. Another study reported a significant elevation of miR-24 in

salivary exosomes from preoperative OSCC patients (N = 45) compared to normal controls (N = 10). MiR-24 has excellent diagnostic accuracy for OSCC, as per the ROC analysis. miR-24 expression was higher in the tissues of OSCC neoplastic, indicating that circulating miR-24 may be derived from tumor cells. Moreover, exogenous exosomal miR-24 enhanced the proliferation of the recipient malignant cells. Additionally, miR-24 promotes OSCC cell proliferation and regulates the expression of cell cycle-related genes. The dual-luciferase reporter assay showed that miR-24 can directly interfere with PER1 and can be a good diagnostic marker [93]. In tongue squamous cell carcinoma (TSCC) patient's, elevated miR-24 levels are correlated with tumor progression and poor prognosis, and enhanced levels of miR-24 *in vitro* correlated with the migration, invasion and proliferation of TSCC cells (UM1, UM2, Cal27, SCC1, SCC15 and SCC25), at least partially through modulation of its target FBXW7. Thus, miR-24 is a novel potential prognostic biomarker for the TSCC patients [94].

Leukaemia (LK)

Upregulated expression of miR-24 has been reported to be associated with poor prognosis [95] in acute myeloid leukaemia (AMLK). MiR-24 was also reported among 63 differentially expressed miRs in AMLK patient's blood samples with NPM1 mutations in comparison to patients with FLT3 mutations [96]. MiR-24 expression levels were detected using qRT-PCR in 84 AMLK patients. The frequency of miR-24 was higher in patients with chromosomal translocation t(8;21) than in others. Mir-24 may be a novel therapeutic target for AMLK with t(8;21) [97]. MiR-24 facilitates AMLK cell growth, interleukin-3 independent proliferation, blocks granulocytic differentiation, suppresses mitogen-activated protein kinase (MAPK) phosphatase-7 and facilitates phosphorylation of c-jun-NH2-kinase and p38 kinases [13]. MiR-24 as well miR-126 and miR-365 have been reported to modulate apoptosis and cell cycle progression in numerous tumor types. The selected candidate target genes identified using the miR-mRNA expression data of 37 children with BCP-ALL for miR-24 (ELL, EBF3 and IRF4), miR-126 (PITPNC1) and miR-365 (ZAP-70), were not reduced by miR overexpression [98]. MiR-24 expression analysis by RT-qPCR showed that the expression of miR-24 with acute leukaemia (ALK) patients (N = 147) was significantly higher than that in healthy individuals (N =100). The higher expression of miR-24 in ALK patients led to shorter overall survival, as per the Kaplan-Meier analysis. MiR-24 has been identified as a prognostic marker for clinical outcomes in patients with ALK [99]. The effects of changes in the expression levels of miR-24, miR-128, miR-542, miR-31, and miR-708 in lymphoid development [early B-cell factor 1, ETS variant 6, paired box 5, IKAROS family zinc finger 1, retinoblastoma 1, pseudoautosomal region 1, cyclin-dependent kinase inhibitor (CDKN) 2A/CDKN2B, B-cell translocation gene 1 protein] were evaluated. Reduced levels of miR-24 were associated with the deletion. PAX5 deletion correlated with low miR-31, miR-24, miR-708 and miR-128 expression. Enhanced miR-24 and miR-542 expression was maintained with PAR1 deletion [100].

Lung cancer (LC)

MiR-24 was significantly upregulated in primary non-small cell lung cancer (NSCLC) specimens and in patient serum. Elevated miR-24 expression in patient serum correlates with a decreased survival rate. Reduction of miR-24 inhibits cell proliferation and anchorage-independent survival ability of LC cell lines and reduces tumor formation in mice [101]. In NSCLC patient samples and cell lines (A549 and H460), miR-24 was significantly overexpressed and promoted invasion in A549 and H460 cell lines by targeting ZNF367 (zinc finger protein 367) [102]. NSCLC patients with tumor node metastasis (TNM) stage I, II, III, IV and NSCLC cell lines (NCI-H358 and NCI-H1299) overexpressing miR-24 had reduced levels of its predicted target WWOX (WW domain-containing oxidoreductase). MiR-24 and WWOX together deregulated activate-caspase-3 and increased the expression of MMP9, promoting invasion [103]. In LC, miR-24 was observed to downregulate SOX7 by a post-transcriptional mechanism, thus promoting cell proliferation and migration in A549 and H1299 cell lines, accelerating tumor growth in a xenograft mice model [104]. MiR-24 was reduced in the etoposide and cisplatin-resistant SCLC cell line (H446/EP) and increased in the VP16-DDP-sensitive parental cell line (H446). MiR-24's forced expression sensitized H446/EP cells to

VP16-DDP treatment by blocking autophagy, particularly ATG4A [105]. MiR-24, miR-22 and miR-34a expression was increased in NSCLC patient samples and can be used as biomarkers for patients non-responsive to pemetrexed [106]. MiR-24 and miR-21 can serve as biomarkers for recurrence of LC after surgery, as their levels before surgery are high and increased levels of miR-24 lead to a low survival rate. Post-surgery, the levels of miR-24 and miR-21 are low and increased levels contribute to the recurrence of LC [107]. Expression levels of cell-free miR-24 and miR-30d were higher in pleural effusions than in benign effusions. The composite of cell-free miR-24 and miR-30d could distinguish malignant ascites with enhanced potency in comparison to single miR-30d [108]. The expression of the TS gene menin was reduced in the LC. MiR-24 regulates menin via SMAD3 pathway [109]. Adenocarcinoma (AC) is the most common subtype of NSCLC. In postoperative biopsies of AC and non-malignant lung samples (NMLTs), SOX18 was suppressed and higher levels of miR-24 and miR-7a were observed. MiR-7a and miR-24 are increasingly expressed in NMLTs than in AC samples, and regulate the SOX18 transcript in NSCLC cells [110]. MiR-24 targets the 3'-UTR-XIAP mRNA and represses its expression and inhibits apoptosis in LC [111].

Lymphoma (LY)

Hodgkin's lymphoma (HL) is a malignant tumor derived from B cells that have high miR-24 expression and reduced DEDD expression in HL tissues compared to adjacent tissues. Cells overexpressing miR-24 showed a notable increase in the invasion of L136 and L428 cells, in contrast to the control. HL cells overexpressing DEDD rescued miR-24-mediated promotion of cell migration and invasion. Collectively, the study reported that DEDD reversed the partial function of miR-24 in HL cells [112]. Small RNA sequencing in HL cell lines revealed 84 differentially expressed miRs compared with germinal center B cells. Three of the upregulated miRs (miR-23a, miR-24, and miR-27a) were derived from the same primary miR transcript. Loss-of-function analyses of these miRs and their seed family members reduced the growth of miR-24 repression in three HL cell lines (L1236, L428, and KM-H2). The results from Ago2-RIP-Chromatin IP suggested that CDKN1B, SIPR1, CARD10, 37 BCL2L11, cMyc, and INSIG1 are targets of miR-24, followed by confirmation by western blot analysis. In summary, miR-24 was upregulated in HL and its inhibition impaired cell growth feasibly by targeting Myc and CDKN1B/P27kip1 [113]. Signature circulating miR-24 from patient serum was increased compared to that in controls and showed identical patterns in murine models. According to the recursive partitioning analysis, five miR signatures (let-7b, -7c, miR-18a, -24, and -15a) were reported with a 91% classification rate for serum with DLBCL diffused patients vs. controls. MiR-24 has also been reported as a useful reference miR in DLBCL studies [114]. In addition, Myc rearrangement has been linked to higher levels of miR-27a and miR-24 [115]. Sandhu et al. and Sole et al. discussed miR-24 along with other miR-based therapies for the diagnosis and treatment of lymphoma [116, 117].

Melanoma (ML)

Ectopic expression of miR-24 acts as a TS and suppresses the migration, invasion, and proliferation of mouse ML cells (B16F10) by directly targeting p130Cas [118]. MiR-24-1 is a candidate miR that is deregulated in cutaneous malignant melanoma (CMM) [119]. The expression levels of miR-24-1 in malignant ML samples, involving primary, metastatic malignant ML, and malignant ML specimens associated with lymph node metastasis (LNM) were lower than those in adjacent normal tissues. ML cells A375, overexpressed with miR-24-1 showed enhanced levels of beclin-1 and LC3-II/I ratio, suggesting autophagy induction. The TargetScan Human database predicted UBD as a target of miR-24-1 and was validated by luciferase-reporter analysis. MiR-24-1 mediated silencing of UBD increased apoptosis and autophagy in melanoma A375 cells. Overexpression of miR-24-1 in A375 cells leads to increased phosphorylation of JNK; thus, the JNK pathway can be involved in miR-24-1-mediated apoptosis and autophagy in A375 cells [120].

Osteosarcoma (OS)

Level's of miR-24 were upregulated in OS cell lines (MG-63 and HOS), tumor tissues and OS patients' serum. In OS cell lines (MG-63 and HOS), knockdown of miR-24 enhanced the

therapeutic effect of doxorubicin by increasing BIM, Smac/DIABLO and mitochondrial apoptosis [121]. Contrary to the above report, miR-24 levels were reduced in OS tissues (N = 84), but the von Willebrand factor (VWF), a target of miR-24, was significantly increased in MG-63 and U2OS cells. MiR-24 repressed the proliferation and migration of MG-63 and U2OS cells and the same effect was observed clinically. Low miR-24 levels in clinical OS tissues are involved with tumor metastasis and reduced survival [122]. TUT1, a nucleotidyl transferase, was found to be downregulated in OS. TUT1 inhibits peroxisome proliferator-activated receptor gamma (PPARγ) and SREBP-1c, which regulate lipogenesis through the upregulation of miR-24 and miR-29a [123]. The target of miR-24, Ack1 was upregulated in OS. This study indicated the repression of miR-24 on OS metastasis by targeting Ack1 through AKT/MMP pathways, furnishing a novel diagnosis and treatment strategy for OS patients [124]. The target of miR-24, lysophosphatidic acid acyltransferase-β (LPAATβ) was downregulated in OS cells. In OS cells, overexpression of miR-24 downregulated LPAATβ expression and inhibited cell proliferation; however, this effect was blocked when LPAATβ activity was inhibited [125].

Pancreatic cancer (PaC)

Elevated levels of miR-24 have been reported in the blood of PaC patients [126, 127]. The expression of miR-24 was substantially changed in PaC and cell lines (ASPC-1, BxPC-3, Hs766T, HPAF-II, Capan-1, Capan-2, Panc-1, MIA PaCa-2, Panc3.27, and PL45) compared with relatively normal pancreatic tissues and HPDE cells [128]. MiR-24 regulates menin in the endocrine pancreas, a TS. In MIN6 insulinoma cells and in lox5 immortalized cells, miR-24 directly reduced the levels of menin expression and impacted downstream cell cycle inhibitors [129]. In 62 patient samples, a panel of nine miR signatures, including miR-24, was suggested to differentiate between high- and low-risk pancreatic cystic neoplasms [130]. Using MAGIA tool and Cytoscape 3 software, miR-mRNA interaction data analysis revealed that miR-24 was the most significantly upregulated and target genes ACVR2B, GFRA1 and MTHFR were found to be downregulated [131]. The repressed expression of Bim was related to the significant upregulation of miR-24 in PaC. It accelerates vascular ring formation and promotes the growth of cancer and vascular cells. *In vivo* (in a tumor mouse model) repression of Bim expression by miR-24 facilitates angiogenesis and tumor growth [132]. In the two groups of PDAC cell lines, adhesion assays indicated a consistent relationship between integration capacity and adhesive properties. MiR-24 and/or miR-23a target TMEM92 and/or FZD5, HNF1B, respectively as per microarray analysis and they are deregulated significantly. MiR-24 and/or miR-23a overexpression led to gene silencing of HNF1B and/or FZD5 and TMEM92. This downregulation facilitates E-cadherin and β-catenin degradation [133].

Prostate cancer (PrC)

MiRs in the miR-23b/27b/24-1 cluster were suppressed in PrC clinical samples. Studies on gain-of-function of all three mature miRs in clusters (miR-23b, -27b and -24) reduced migration, invasion and proliferation in PrC cell lines (PC3 and DU145) [134]. The incidence of PrC is significantly higher among African-Americans (AfA) than among Caucasian-Americans (CaA). In patients with AfA and CaA, miR-24 was differentially expressed. The miR-24 promoter is methylated and therefore, miR-24 is downregulated in PrC patients. In an AfA cell line (MDA-PCa-2b), miR-24 levels were restored after treatment with 5Aza-CdR. However, miR-24 level restoration was not noticed in CaA cells (DU-145). Transient overexpression of miR-24 diminished cell growth and promoted apoptosis in AfA cell lines, although the effect was less in the CaA cell line [135]. MiR-24 also regulates apoptosis by targeting FAF1 in cancer cells (DU-145) [136]. Decreased expression of miR-24 was observed in both the needle core and prostatectomy tumor tissues relative to normal tissues. Low expression levels of miR-24 are associated with high prostate-specific antigen (PSA) levels in serum. Importantly, enhanced expression of miR-24 abrogated the cell cycle, migration, proliferation and clonogenic potential of prostate cancer cells, along with the induction of apoptosis. A significant inverse correlation between miR-24 and p27 has been observed in clinical prostatectomy specimens [137]. The diagnostic three-miR model (miR-222-3p* miR-24-3p/miR-30c-5p) markedly distinguished prostatic hyperplasia (BPH) and PrC

patients predicted in different cohorts [138]. Lin et al. reported the tumor-enhancing role of miR-24 in PrC and observed upregulation of miR-24 in PrC cell lines (LNCaPFGC, PC3 and DU 145). This overexpression promoted cell proliferation, inhibited apoptosis, and increased cell migration and invasion. SOCS6 is a direct target of miR-24 and overexpression of SOCS6 (suppressor of cytokine signaling 6) reverses the effects of miR-24 on the metastatic phenotype of PrC cells [139]. In recurrent prostate tumors, miR-24-1 was reported to be one of the downregulated miR [140].

Retinoblastoma (Rb)

Review papers have reported the roles of ncRNAs and miRNAs in Rb [141, 142]. In human Rb tissues and cell lines (RB 247, 381, 1021, WERI-Rb1, Y79, B247 and RB381), p14ARF was disproportionally increased at the RNA level and not at the protein level. Overexpression of p14ARF led to an increase in the expression levels of p53 and therefore, apoptosis. This discrepancy between p14ARF mRNA and protein in Rb was caused by miR-24 as it represses the expression of p14ARF, is heavily upregulated in Rb cell lines and correlates with lower expression of p14ARF in various cell lines (HeLa, HEK-T, SaOS-2 and OVCAR-3) with high p14ARF mRNA [143]. The antisense ncRNA in the INK4 locus (ANRIL) was overexpressed in Rb tissues and cells (Y79) responsible for the viability, migration and invasion of Rb Y79 cells. ANRIL is negatively regulated by miR-24 and positively regulated by cMyc, which is a target of miR-24 [144]. Microarray profiling of three Rb and control samples indicated that seven miRs (let-7b, -7c, -24, -125b, -191, -181a and -423) expression levels were repressed in Rb [145].

Various cell lines

MiR-24 promotes the HEKa cells proliferation. Both $p27^{Kip1}$ (p27) and $p16^{Ink4a}$ (p16) had probable seeding sequences for miR-24. Among various cell lines [CC cell lines (SiHa, CaSki, and ME-180), BRC cell lines (CAMA, T47D, HBL-100), LC cell lines (A549, H1299), GC cell line (AGS) and thyroid carcinoma-derived cell line (TPC-1)], overexpression of miR-24 suppressed p27 at various levels in almost all cell lines, except for T47D and A549 cells. In the other cell lines, a reduction in p16 protein levels with p27 downregulation was observed, with the exception in the cell lines SiHa, TPC1, H1299, and T47D. MiR-24 significantly increased AGS TPC1, H1299, SiHa and CaSki cell proliferation. HBL100, CAMA and ME-180 had a smaller induction of miR-24-mediated proliferation compared to a minor reduction in p27 protein levels [146]. A study of miR-24 in BRC (SK-BR-3 and MDA-MB-468), NSCLC (A549, H1437, CALU-1 and H292), and CC (HeLa) cell lines reported that miR-24 is a candidate regulator of XIAP expression. In various cell lines (A549, OE21, H292, HeLa, SK-BR-3, and MDA-MB-468) significantly reduced XIAP protein levels increase the sensitivity to TRAIL-induced cytotoxicity. Caspase-3 activity was significantly upregulated in A549 and H292 cell lines by combining miR-24 overexpression and TRAIL [111]. By modulating different apoptotic pathways and targeting BCL-2, miR-24-2 is capable of inducing apoptosis and an anti-apoptotic gene. In the MCF7 and HeLa cell lines, In spite of change in copy number, H2AX gene expression effectively controlled by miR-24-2. This study further signifies that combination therapy using anticancer drugs, such as cisplatin, along with miR-24-2 [42]. HPV oncoproteins have been reported to alter the levels of miR-205 and miR-24 in HFK cells. E7 and E6 expressions stimulate miR-24 and is suggested to facilitate cell proliferation by regulating the cell cycle inhibitor p27 [147]; Deregulated levels of miR-24 suppressed the invasion and proliferation of PC-3, B16F10, MCF7 SK-Hep1, and Hep3B cells via the miR-24/p130Cas axis [118]. MiR-24 and miR-24-2 have been suggested as anti-pluripotent and epigenetic stemness-regulatory miRs. The interplay between PRMT7 (protein arginine methyltransferase 7)/MiR-24/miR-24-2 feedback loop with Oct4, Nanog, Klf4 and cMyc has been reported to control the stemness of mouse embryonic stem cells (ESCs) [148]. MiR-24 targets the prolyl hydroxylase domain (PHD1). Thrombin-mediated upregulation of miR-24-1 reduces HIF-1α degradation and initiates angiogenesis in intracerebral hemorrhagic rats [149]. MiR-24 is reported as a p53-independent G2/S cell cycle inhibitor and possesses anti-proliferative activity in human OS (U-2 OS, MG63, RKO and HT-29), human colon cancer [HCT 116 (null-p53) and HCT 116 (wt-p53)] cell lines [48]. During differentiation into megakaryocytes, erythrocytes, macrophages, monocytes, and granulocytes, a 2- to 8-fold increase in miR-24

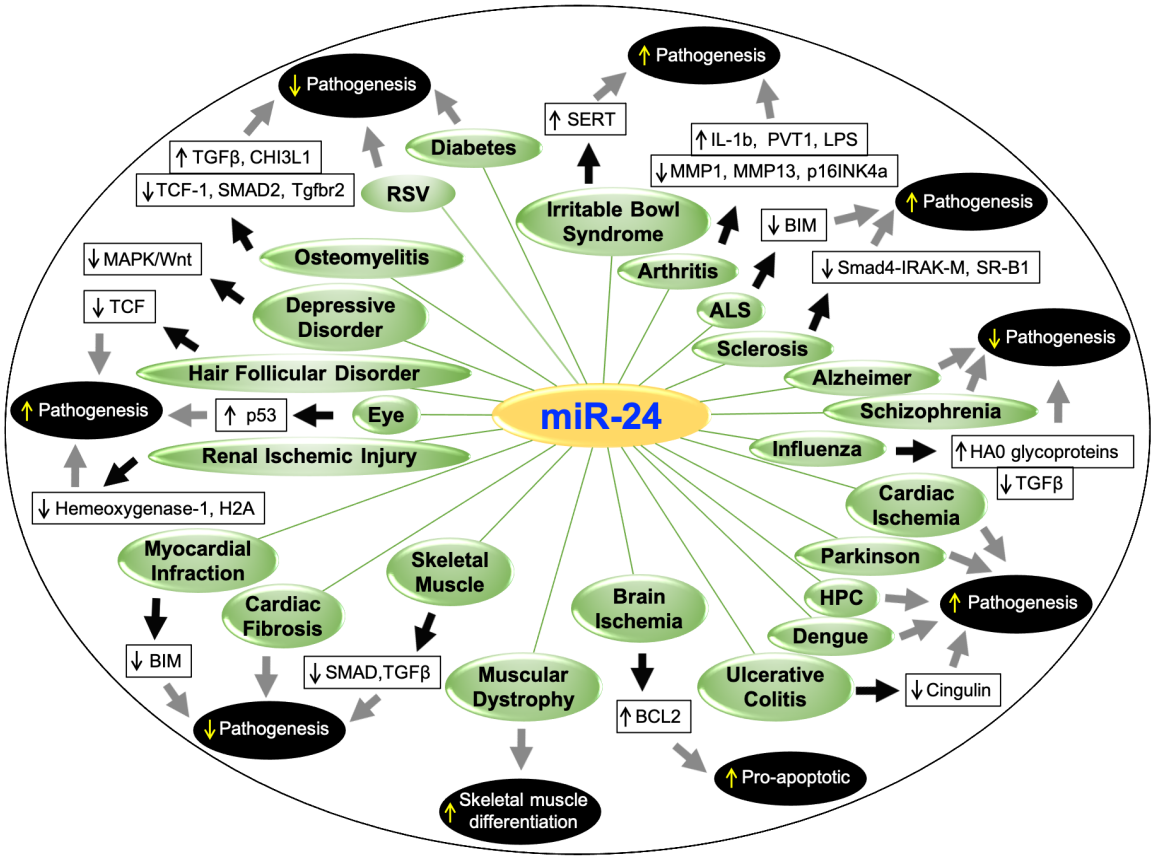

Figure 5. Schematic representation of target genes, regulatory pathways and interactive functions of miR-24 in different diseases. Black thick arrow directed the regulatory genes. Gray thick arrow indicates the regulatory phenotypes and biological functions. Black thin arrow pointed upward and downward indicate the upregulation and downregulation of the corresponding gene's expression, respectively. Yellow arrow pointed upward and downward indicate the upregulation and downregulation of the corresponding biological functions, respectively.

transcript level was observed. MiR-24 was further reported to inhibits cell cycle progression, facilitates the proliferation of fibroblasts and regulates E2F2, Myc, AURKB, CCNA2, CDC2, CDK4, and FEN1 in K562 and HepG2 cells [150].

MiR-24 and other diseases

Similar to cancer, miR-24 is deregulated in several other human diseases. Herein, we summarized the deregulated expression of miR-24 (**Figure 5** and **Table 4**), miR-24-1 (**Figure 4** and **Table 2**) and miR-24-2 (**Figure 4** and **Table 3**) and its association with different human diseases.

Arthritis

The combination of three miRs (miR-24, -26a, and -125a-5p), named as "estimated probability of Rheumatoid arthritis (RA) by plasma miRs" (e-PRAM), was recommended for use as a potential biomarker for the recognition of RA patients [151]. Employing miR-24, -30a-5p and -125a-5p provided a formula for ePRAM, which has shown increased diagnostic accuracy. Compared to RA patients, the levels of miR-24, -125a-5p, and ePRAM in systemic lupus erythematosus (SLE) and osteoarthritis (OA) patients were lower [152]. MiR-24 is a negative regulator of $p16^{INK4a}$. Overexpression of $p16^{Ink4a}$ in chondrocytes induced the generation of two matrix remodeling enzymes (MMP1 and MMP13), linking senescence with bone development and OA pathogenesis [153]. Li et al. reported in ATDC5 cell depletion of one lncRNA, plasmacytoma variant translocation 1 (PVT1), protects the cartilage against LPS-induced inflammatory injury through the miR-24/ADAMTS5 axis, opening up a novel avenue for

Table 4. Deregulated expression of miR-24 and its regulatory genes in other diseases

Diseases	Up/Down (MiR-24)	Regulatory genes/pathways		Regulatory biological functions	Tissue/Sample type
		Upregulated	Downregulated		
Arthritis	Up in RA	IL-1β PVT1, LPS	MMP1, MMP1, $p16^{INK4a}$	Senescence, Cartilage, chondrogenesis cell viability, apoptosis, secretion of inflammatory cytokines	Patient, ATDC5
Bone Disorders	Down in osteomyelitis	TGFβ, CHI3L1	TCF-1, SMAD2, TGFBR2	Bone formation or differentiation osteoporosis pathogenesis or bone remodeling, skeletal muscle fibrosis	Patient, MC3T3-E1
Cardiovascular Disorders	Up in ischemia, RIPC and heart failure down in thrombotic cardiovascular events, myocardial infraction; Down in I/R injury	Aldose reductase, reactive oxygen species, cMyc. Keap1-Nrf2	GATA2, PAK4, BIM, PDGFRB, CHI3I1, SCN5A, PKC-delta, JP2, BIM, ESCA, ADL, LVEF and SF-36, Chi3l1	Smooth muscle cells (SMC) migration, Fibrosis, vascular inflammation and abdominal aortic aneurysm (AAA) pathology, heart failure mortality, proliferation ability of cardiomyocytes Apoptosis, proliferation, hydroxyproline synthesis, angiotensin II	Mice model, H9C2, Rat cardiac fibroblasts (CFs), PDGFRB
Eye Disorders	Up in cataract, AMD, TM	TGFβ	p53, subtilisin-like proprotein	Age-associated cataractogenesis, glaucoma	Patient and SRA01/04 cells
Diabetes	Up in early onset of T1D, down in T2D	Willebrand factor, aldose reductase reactive oxygen species, and cMyc	CHI3I1, insulin promoter, Hnf1a, SFRP4 and Neurod1	Diabetic myocardial I/R and increased infarct size post-I/R, diabetic foot ulcer, diabetic foot osteomyelitis	Patient
Gastrointestinal & Liver Diseases	Up in IBS, ulcerative colitis	Menin and TGFβ	Cingulin, BIM, STING	Trans-epithelial electrical resistance and increased dextran flux, hepatocyte apoptosis, hepatic lipid accumulation and reduced plasma triglycerides, cellular apoptosis in hepatic I/R process	Mice model, mucosal epithelial cell line, patient
Hair	Up-regulated		TCF-3	Anti-proliferative, hair morphogenesis	Mice model
Muscular dystrophy	Up after exercise, down during relaxation	TGFβ, MHC, MEF2, Myogenin	PDGFRB, p38, SMAD2 and TGFBR2	Myoblast differentiation, SMC migration and proliferation	Murine model, patient
Neurological Disorders	Down in early Alzheimer stage, ADHD and Schizophrenia up in Parkinson's diseases	-	XIAP, HPCA	Alzheimer disease (AD), Parkinson, neuron cell apoptosis, neurona, HPCA expression I differentiation	CSF and blood from, SH-SY5Y cells
Renal and Urinary System Disorders	Up	-	H2A histone family, member X, and heme oxygenase 1	Apoptosis, hypoxic conditions, renal ischemic injury	Mice model, patient,
Sclerosis	Up	-	SMAD4-IRAK-M, SR-B1	Disability progression index, inflammation and atherosclerosis	Patient
Syndrome	Down in PCOS	-	-		293T, SHSY5Y cell lines and Patient
Viral related Diseases	Down in Dengue, RSV, PRRSV, Influenza	KLF6, TGFβ, NS1	PCSK9	PRRSV replication, activation of HA0 glycoproteins and production of infectious virions, HBV replication, lipid homeostasis	Patient

RA: Rheumatoid arthritis; RIPC: Remote ischaemic preconditioning; I/R: Ischemia/Reperfusion; AMD: Age-related macular degeneration; TM: Trabecular Meshwork; T1D: Type 1 diabetes mellitus; T2D: Type 2 diabetes mellitus; IBS: Irritable Bowel Syndrome; ADHD: Attention-deficit/hyperactivity disorder; PCOS: Polycystic ovary syndrome; RSV: Human respiratory syncytial virus; PRRSV: Porcine Reproductive and Respiratory Syndrome Virus.

OA therapeutics [154]. Wang et al. reported 40 miRs (22 downregulated and 18 upregulated) that were differentially expressed in the RA samples compared to the healthy controls (HCs) and miR-24 is one of 18 upregulated miRs (fold change ~2.0679) [155]. Significantly increased expression of miR-24, along with six other miRs were observed in IL-1β-stimulation OA synovial explants [156].

Bone disorders

Osteomyelitis is an infectious disease of the bone that is mainly induced by *Staphylococcus aureus.* Analysis of the entire blood of patients with bacterial osteomyelitis, healthy controls and *S. aureus* infected MC3T3-E1 cells showed downregulation of miR-24 compared to the healthy controls or untreated control cells. However, the effects of *S. aureus* could be reduced by overexpression of miR-24, while inhibition of miR-24 intensified the effect [157]. MiR-24 was among one of the up-regulated miRs in osteoporotic fracture patients [158-161]. Zhao et al. reported that miR-24 significantly inhibits osteogenic differentiation and regulates T-cell factor-1 (Tcf-1) expression by targeting the 3'-UTR of Tcf-1 mRNA in bone mesenchymal stem cells and murine osteoprogenitor cells [162, 163]. Kelch et al. reported a correlation between miR-24, miR-21-5p, miR-100-5p, miR125b-5p and miR-93-5p, with bone mineral density (BMD) [164]. Yavropoulou et al. studied the expression of 14 miRs (miR-21-5p, 23a-3p, 24-2-5p, 26a-5p, 29a-3p, 33a-5p, 124-3p, 135b-5p, 214-3p, 218-5p, 335-5p, 2861, 1331-3p, 422a) in osteoporotic/osteopenic patients with low bone mass and vertebral fractures (VFs) and compared them with patients without VFs [165]. Sansoni et al. studied the effects of an eight-week repeated sprint training on circulating miRs. MiR-23a and miR-24 expressions were observed to decreases significantly after 4- and 8-weeks compared to age-matched inactive controls [166]. In skeletal muscle fibrosis, the TGF-β/Smad signaling pathway was identified as a pathologically positive feedback loop and two miRs (miR-24 and -122) act as fibrogenic inhibitors that downregulate Smad2 and Tgfbr2 levels, respectively [167]. In addition, the effect of miRs on osteogenic differentiation was studied by analysing Runx2, osteocalcin, osteonectin and alkaline phosphatase (ALP) expression. Studies performed on the 7th day after induction of osteogenic differentiation and Alizarin Red staining mediated calcium deposition after 21 days. The data revealed that the effects of let-7g, miR-21 and miR-24 were donor-dependent [168, 169]. SATB2 is a key regulator of skeletal development. Hassan et al. reported a regulatory network of SATB2 and miR-23a-27a-24-2 cluster as regulators of the progression and maintenance of the osteocyte phenotype [170].

Cardiovascular diseases

MiR-24 induces cardiac endothelial cell apoptosis, abolishes endothelial capillary network formation on Matrigel and inhibits cell sprouting from endothelial spheroids by targeting GATA2 and PAK4. Inhibition of endothelial miR-24 limits myocardial infarction in mice [171]. Hyperglycemia-induced reduction of miR-24 increases levels of VWF and secretion in diabetes mellitus and increases the risk of thrombotic cardiovascular events [172]. MiR-24 suppresses apoptosis in cardiomyocytes by repressing the BH3-only domain-containing protein Bim, which activates apoptosis. In the MI model, the *in vivo* expression of miR-24 inhibited apoptosis, diminished cardiac dysfunction and mitigated infarct size [173]. The Myh6-miR-24 transgenic mice under normal physiological conditions did not show an apparent difference from their wild-type littermates. However, when subjected to myocardial infarction (MI), the transgenic mice indicated reduction in cardiomyocyte apoptosis with enhanced cardiac function and decreased scar size post-MI compared to their wild-type littermates [174]. MiR-24 regulates JP2 expression by binding to at least one of the two sites within the 3'-UTR of JP2 mRNA. MiR-24 overexpression leads to ultrastructural remodeling of TT-SR and defective E-C (excitation-contraction) coupling, reproducing those found in failing heart cells [175]. MiR-24 and miR-155 levels in serum are inversely related to the ADL, ESCA, LVEF and SF-36 scores, and affect the quality of life. Tai Chi treatment improved CHD prognosis by regulating miR-24 and miR-155 in the serum [176]. MiR-24 inhibits apoptosis initiation by suppressing the release of cytochrome C and translocation of Bax to mitochondria from the cytosol [177]. MiR-24 was present in RIPC (remote ischaemic preconditioning)-induced exosomes and helped to reduce oxidative

stress-mediated injury. In H2O2-treated H9c2 cells, apoptosis was reduced by repressing Bim expression *in vitro*. *In vivo*, miR-24 in RIPC-induced exosomes inhibited cardiomyocyte apoptosis, reduced infarct size and improved heart function [178]. Myocardin-induced miR-24 and miR-29a expressions were reported to regulate PDGFRB, and antagonizing these miRs restored the migration of SMCs. MiR-24 has an indirect effect on PDGFRB levels [179]. In addition, hypoxamir-24 has been elucidated as an inhibitor of SMC proliferation and is associated with loss of vascularization [180]. After 2 and 4 weeks of cardiac infarction, miR-24 expression was significantly repressed ($P< 0.05$). The mRNA levels of Furin and TGF-β1 were elevated after infarction. The miR-24 level was correlated positively with left ventricular systolic diameter, left ventricular end-diastolic diameter and left ventricular ejection fraction [181]. Mir-24 also negatively regulates fibrosis after infarction [182]. Sayed et al. reported that miR-24 is a progressively deregulated miR during pressure-overload cardiac hypertrophy and is downregulated during the later stage of hypertrophy (14 days post-transverse aortic constriction) [183]. MiR-24 has also been reported as a potential circulating biomarker for myocardial infarction and a key regulator of vascular inflammation and abdominal aortic aneurysm (AAA) pathology in two murine models. The study also revealed that chitinase 3-like 1 (Chi3l1) is a known target and inducer under the control of miR-24 [184]. A recent report showed that miR24 suppresses SCN5A expression and synonymous SNPs (rs1805126) near the miR-24 site within the coding sequences of SCN5A alters SCN5A-miR-24 interaction and increases heart failure mortality [185]. A review paper also reported novel therapeutic applications of the miR-23-27-24 cluster in ischemic heart disease and vascular disorders [186]. Mir-24 has been also reported to be associated with type 2 diabetes mellitus (T2D) associated with coronary heart disease (CHD) [187]. Upregulated miR-24 expression disrupts the function of smooth muscle cells. H9c2 cells transfected with anti-miR-24 significantly decreased the proliferation ability of cardiomyocytes and increased the expression of target gene TGF-β [188]. Downregulated expression of miR-24 in a myocardial ischemia/reperfusion (I/R) injury mouse model diminished I/R injury by targeting RIPK1 expression in mice [189]. Another study also reported downregulated expression of mir-24 associated with I/R injury in mice hearts and was associated with apoptosis of cardiomyocytes by targeting the Keap1-Nrf2 pathway [190]. MiR-24 induces apoptosis and inhibits proliferation, hydroxyproline synthesis and myocardial fibrosis induced by angiotensin II by negatively regulating PKC-delta through the AGTR1-Gq-PKC signaling pathway [191].

Diabetes

Deregulated expression of miR-24 has been reported in both type 1 diabetes mellitus (T1D) and type 2 diabetes mellitus (T2D) [192-194]. Thirty-five miRs were significantly different in the sera of children with T1D compared to age-matched controls and among these, 27 miRs were elevated. Good distinctive power was obtained for six miRs, including miR-24, in a larger cohort (beyond 90 days after diagnosis) [195]. Global miR sequencing analyses identified 12 enhanced miRs, including miR-24, in T1D patients. Several of these are connected to apoptosis and beta-cell networks [196]. MiR-24 and miR-29b expression was distinguishable in type 2 diabetes mellitus patients and controls after adjustment for sex, age, family history of T2D, waist circumference, and a sedentary lifestyle [197]. Plasma samples from 47 T2D patients who received no anti-diabetic treatments and 47 T2D patients who received three months of metformin treatment were screened for the expression of thirteen potential miRs. MiR-24 was found to be significantly reduced after metformin treatment in patients with T2D [198]. In the diabetic heart, miR-24 reduction and O-GlcNAcylation induced by hyperglycemia and hyperinsulinemia lead to poor survival in diabetic myocardial I/R and enhanced infarct size post-I/R. MiR-24 has also been suggested as a potential therapeutic target for post-infarct healing in T2D patients [199, 200]. In diabetic patients, acute myocardial infarction (MI) is correlated with subsequent increased heart failure, mortality and myocardial dysfunction after acute myocardial infarction (MI) in T2D was reported due to the deregulation of miR-24 [201]. Significantly downregulated expression of circulating miR-24 was reported in the peripheral blood of T2D associated coronary heart diseases (T2D-CHD) patients in comparison to controls. They also

reported that miR-24 mediates the regulation of YKL-40 [chitinase 3-like 1 (Chi3l1)] in T2D-CHD and may serve as a biomarker for predicting T2D-CHO patients [187]. Plasma levels of miR-24 in diabetes are notably lower than those in healthy controls [172]. MiR-24 tightly regulates VWF (von Willebrand factor) levels through pleiotropic effects (e.g., binding to the 3'-UTR of VWF to target FURIN and the histamine H1 receptor). Xiang et al. reported miR-24 as a novel therapeutic target for the prevention of adverse thrombotic events in patients with diabetes mellitus in VWF-induced pathology [172]. Melkman-Zehavi et al. reported knockdown of miR-24 along with other three miRs (miR-26, miR-182 and miR-148), downregulate insulin promoter activity and insulin mRNA levels in β-cells or in isolated primary islets using adult mice [202]. Increased expression of miR-24 was reported to stop insulin secretion and β-cell proliferation and identified the miR-24/MODY gene regulatory pathway as a novel network for the study of T2D [203]. Elevated expression of miR-24 along with two other miRs (miR-30d and miR-146a) and antiangiogenic factor secreted frizzled-related protein 4 (SFRP4) were reported to be correlated with obesity and insulin resistance in T2D reported in human abdominal adipose tissue [204]. A study conducted at Florida Hospital reported that miRs, including miR-24 and miR-375 were linked to β-cell injury [205]. A recent study reported that in T2D patients, expression of miR-24 in the peripheral plasma is correlated with the onset of diabetic foot osteomyelitis (DFO) and diabetic foot ulcer (DFU) [206].

Eye disorders

Oxidative stress in cataract patient samples and the human lens epithelial cell line (SRA01/04 cells) upregulates miR-24 and facilitates LEC death by directly binding to p53 [207]. Age-related macular degeneration (AMD) is a late-onset, progressive, multifactorial neurodegenerative disease of the human retina. A pioneering clinical study on the expression profiling of 384 miRs in the plasma of 33 patients (22 males, 11 females) between AMD and healthy controls reported that miR-24 is one of five upregulated miRs in AMD patients [208, 209]. CMS mediated the expression of miR-24, which led to the repression of the subtilisin-like proprotein convertase FURIN, a key player in the processing of TGFβ1. Luna et al. reported that miR-24 plays an important role in the flow pathway by regulating TGFβ1 induction mediated by CMS via direct binding of FURIN [208, 210].

Gastrointestinal & liver diseases

In the proximal colon of IBS (irritable bowel syndrome), studies using mice confirmed that treatment with the miR-24 inhibitor elevated the threshold of pain and nociception, diminished activity of MPO, and upregulated expression levels of SERT mRNA and protein in intestinal mucosa epithelial cells [211]. Upregulated expression of miR-24 has been reported in ulcerative colitis (UC) patient's colonic biopsies and blood samples than in healthy controls. MiR-24 is localized to intestinal epithelial cells in the colon of UC patients. Overexpression of miR-24 in both Caco-2 and T84 cell lines led to enhanced dextran flux and reduced transepithelial electrical resistance. Overexpression of miR-24 did not affect apoptosis or cell proliferation. This also suggests that the miR-24's effect on barrier function might be due to its effect on cell-to-cell junctions [212]. MiR-24 indirectly reduced D-GalN/LPS challenge *in vivo* and D-galactosamine/tumor necrosis factor (D-GalN/TNF) challenge *in vitro*. In D-GalN/TNF-treated BNLCL2 cells, miR-24 overexpression inhibited apoptosis and attenuated BIM mRNA and protein levels *in vitro*. Taken together, the study demonstrated that during ALF development via BIM, miR-24 regulates hepatocyte apoptosis [213]. The expression of miR-24 was notably upregulated in the livers of mice treated with a high-fat diet and incubated with isolated human hepatocytes with fatty acids. MiR-24 knockdown in these mice diminished hepatic lipid accretion and plasma triglyceride levels [214]. Silencing of miR-24 enhances menin a histone modifier and TGFβ expression. Subsequently, in FVB/NJ WT and Mdr2$^{-/-}$ mice, hepatic fibrosis was increased [215]. STING mRNA levels were inversely correlated with miR-24 levels in the livers of I/R-treated mice. By targeting STING, miR-24 may boost cellular apoptosis and inflammatory response in the hepatic I/R process, indicating its potential as a therapeutic agent for the treatment of liver I/R development and progression [216].

Hair

Transgenic mice transiently expressing miR-24 under the K5 promoter displayed a defect in hair follicle (HF) morphogenesis, with thinning

of the hair coat and altered HF morphology. MiR-24 directly reduces the regulator of hair keratinocyte stemness by targeting Tcf-3 [217]. Comprehensive analysis of ten miRs (miR-31, 24, 106a, 22, 125b, 137, 205, 214, 221 and 410) in human HF identified their target genes. Furthermore, a significant correlation between miR-24 and six collagen genes (in descending order of significance: COL5A2, COL17A1, COL4A6, COL4A5, COL18A1 and COL4A1) suggested an important regulatory role of miR-24 in hair morphogenesis and maintenance via the control of integrin and collagen signaling [218].

Muscular dystrophy

Several studies have reported the regulatory role of miR-24 in muscular dystrophy [219-223]. Circulatory miR-181a-5p, miR-27a-5p and miR-24-2 were upregulated shortly after exercise, followed by downregulation during relaxation [222, 223]. Sun et al. revealed miR-24 mediated modulation of TGF-β-dependent inhibition of myoblast differentiation as a novel molecular mechanism underlying skeletal muscle differentiation. They also reported the importance of Smad3 and a Smad binding site in the miR-24 promoter region for the repression of miR-24 transcription by TGF-β1 [224]. MiR-24 is one of the upregulated miRs during cardiac hypertrophy, capable of inducing hypertrophic growth *in vitro* and embryonic lethality [225, 226]. Talasila et al. reported it as a key regulator of the neointimal response that impedes the vascular injury response in murine carotid arteries and reduces smooth muscle cell (SMC) migration and proliferation via a novel mechanism that involves induction of miR-24 and miR-29a and repression of the PDGFRB pathway [179]. MiR-24 also contributes to the loss of vascularization by inhibiting SMC proliferation [180]. The miR-23a-27a-24-2 cluster has also been reported to be a regulator of cardiac hypertrophy and skeletal muscles [227]. Local mIGF1 expression regulates miR-24 and miR-206, which confers robustness to dystrophic muscle in mdx dystrophic mice [228]. MiR-24 is downregulated in human arteries with arteriosclerosis obliterans (ASO) and modulates the human arterial smooth muscle cell's (HASMC's) proliferation and migration through PDGF-BB/miR-24/PDGFRB and PDGF-BB/miR-24/cMyc pathways by upregulating target genes platelet-derived growth factor receptor B (PDGFRB) and cMyc [229]. MiR-24 downregulation significantly reduced myogenic markers such as myogenin, MHC and MEF2, and thereafter inhibited the formation of myotubes [224]. Downregulated expression of miR-24 in the skeletal muscle of diabetic rats was associated with an increased expression of p38 MAPK [231]. MiR-24 and miR-122 downregulate the TGF-β/Smad signaling pathway in skeletal muscle fibrosis and act as fibrogenic inhibitors. MiR-24 and miR-122 reduced the levels of Smad2 and Tgfbr2, respectively. However, Smad4 repressed the expression of both miRs [167]. A recent report demonstrated the precise effect of miR-23-27-24 clusters on endurance-exercise-induced muscle adaptation and skeletal muscle development [224].

Neurological disorders

Deregulated expression of miR-24 is associated with several neurological disorders, such as Alzheimer, Parkinson, schizophrenia and spinocerebellar ataxia [233]. Increased miR-24 levels in the cerebrospinal fluid (CSF) are negatively correlated with cell number. In CSF, the addition of blood miR-16, miR-24, and miR-146a expression was vigorously influenced [234]. MiR-24 is downregulated in the white matter of patients with early Alzheimer [235]. AD-associated SNPs present in the amyloid precursor protein (APP) 3'-UTR could also directly influence miR function and Aβ peptide production. MiR-24, along with miR-186, and miR-455 have been identified as regulators of the expression of nicastrin variants (NSCTN; comprising SNPs rs113810300 and rs-141849450), both under physiological conditions in human cells and *in vitro*, leading to altered Aβ secretion [236]. MiR-24 was also reported to be significantly upregulated among 20 differentially expressed miRs in patients with Alzheimer disease [237]. Serum samples from 109 patients with Parkinson's disease (PD) and aged 40 years and sex-matched healthy controls for RNAs encapsulated in exosome-like microvesicles revealed that miR-24, miR-19b and miR-195 in serum are important for the diagnosis of PD [238]. In another study, ten miRs expression was analyzed in CSF for PD and multiple system atrophy (MSA). Among these, the expression of two miRs (miR-24 and miR-205) in PD and four miRs (miR-19a, -19b,

-24, and -34c) in MSA were different from those in controls [239]. The expression levels of miR-19b-3p and miR-24 are positively associated with the progression of PD pathogenesis compared to related multiple system atrophy [240, 241]. In PD, miR-24 was observed to be upregulated in blood and exosomes and downregulated in CSF [242] and has the potential to serve as a biomarker [243]. Four differentially expressed miRs (downregulated: miR-339-5p and upregulated: miR-223*, miR-324-3p, and mir-24) were reported in PD and multiple system atrophy (MSA) patients vs. controls. Further comparison between MSA and PD identified miR-24, miR-34b, and miR-148b upregulation in MSA serum [244, 245]. Lower levels of pri-miR transcripts [miR-24, -26b, -9*, -30e and -7] were observed in patients with schizophrenia [246]. MiR-24 is differentially expressed in plasma-derived exosomal miRs in spinocerebellar ataxia type 3 (SCA3) [247]. Another study reported that miR-24 is one of the significantly deregulated miRs in Friedreich's ataxia (FRDA) compared to healthy controls [248]. Among the 52 ADHD (attention-deficit/hyperactivity disorder) research samples and 52 healthy volunteer controls, there was no significant difference in age or sex. Statistically, significantly decreased levels of miR-24 have been reported [249]. Small RNA-sequencing of paired samples from patients with major depressive disorder (MDD) enrolled in a large, randomized placebo-controlled trial of duloxetine discriminated the expression of four miRs (miR-24, -146a-5p, -146b-5p and miR-425-3p) according to treatment response. These miRs were observed to deregulate the MAPK/Wnt signaling pathway [250]. For ischemic brain disease neurocan and miR-24 have been reported to be potential therapeutic targets. Overexpression of miR-24 or neurocan silencing in SH-SY5Y cells showed an anti-hypoxic effect and played crucial roles in neuronal apoptosis [251]. Using mouse N2A neuroblastoma cells, an oxygen-glucose deprivation (OGD) model was developed. It showed lower levels of plasma miR-21 and miR-24 in patients with acute cerebral infarction (ACI) compared to controls. Gain of miR-24 function in N2A cells led to downregulation of X-linked inhibitor of apoptosis protein (XIAP) [252]. MiR-24 binds to the 3'-UTR of HPCA and regulates neuronal differentiation by controlling Hippocalcin (HPCA) expression [253]. A recent study in rat models of chronic constriction injury (CCI) reported the role of the ZRANB1/miR-24/LPAR3/Wnt5a/β-Catenin signaling axis in the progression of neuropathic pain [254]. Mir-24-2 was reported as one of twelve deregulated miRs in end-stage amyotrophic lateral sclerosis (ALS) mouse and rat spinal cords in comparison to age-matched non-transgenic (non-TG) controls [255].

Renal and urinary system disorders

Post kidney transplantation in mice and patients after I/R injury, elevated expression of miR-24 was observed. After I/R induction revealed, anoxia/hypoxia-induced miR-24 enrichment in tubular epithelial and renal endothelial cells *in vitro*. Transient miR-24 expression facilitates apoptosis and also amended functional parameters of these cell's. In contrast, miR-24 silencing improved the response towards apoptotic and retrieved the hypoxia-related functional parameters. MiR-24's effects were imparted through the modulation of the H2A histone family, member X, and heme oxygenase 1 as direct miR-24 targets. MiR-24 mediated stimulation of apoptosis in endothelial and tubular epithelial cells promotes renal ischemic injury by stimulating apoptosis in endothelial and tubular epithelial cells. Hence, for the treatment of patients with ischemic AKI, miR-24 inhibition could be a promising therapeutic approach in the future [256]. MiR-24 was also upregulated in patients with focal segmental glomerulosclerosis (FSGS) than in patients with diabetic nephropathy (DN) [257].

Sclerosis

Expression profiling of 84 circulating miRs detected upregulated expression of miR-128-3p and miR-24 in primary progressive multiple sclerosis (PPMS) compared to controls and secondary progressive multiple sclerosis SPMS [258]. Another study reported, miR-191-5p and miR-24 were overexpressed in relapsing-remitting multiple sclerosis (RRMS) and PPMS [53 RRMS and 20 PPMS]. MiR-24 was positively correlated with the disability progression index in the combined group of all patients with multiple sclerosis (MS) [259]. Genetic variations in miR coding genes can alter the expression levels of miR. The predicted target genes of miR-23a, miR-24, miR-27a and miR-223 are involved in the pathology and immunity of MS [260]. MiR-24 and miR-137 were significantly deregu-

lated in MS patients compared to the controls and were considered as candidate biomarkers for MS [261]. Induced miR-24 expression by endotoxin regulates Smad4-IRAK-M, a negative feedback modulator of inflammation and downregulates the lipid-processing molecule SR-B1, which contributes to non-resolving low-grade inflammation and atherosclerosis [262].

Syndrome

Hirschsprung disease (HSCR) is a congenital disorder. This is caused by defective activity of the embryonic enteric neural crest. The target genes, ARP2 and ARP3 were downregulated by upregulated miR-24-1 and let-7a*, respectively, in HSCR samples (N = 70) compared to normal controls (N = 74). This study demonstrates a new pathogenic mechanism of HSCR that is associated with the miR-24-1/let-7a*-ARP2/3 complex-RAC isoform pathway [263]. MiR-24, 29a, 151-3p and 574-3p expression is downregulated in women with polycystic ovary syndrome (PCOS), both normoandrogenic and hyperandrogenic [264]. The SNPs of the Rab-5B (RAB5B) genes (rs1045435, rs11550558, rs705700, and rs11171718) were associated with PCOS risk. The study also speculated that the rs1045435 locus is likely to be a miR-24 binding site and rs11550558, rs705700 and rs11171718 may be binding sites for miR-320 [265].

Viral related diseases

MiR-24-1, miR-512-5p and miR-4640-3p expression levels were able to differentiate mild dengue from those displaying liver complications [266]. Pong et al. reported miR-24 as one of the significantly downregulated (1.3 fold) miR in the livers of DENV-1-infected mice compared to uninfected controls [267]. RSV (human respiratory syncytial virus) non-structural protein (NS1) represses miR-24 levels during infection. Lack of NS1 was able to induce the expression of miR-24, while overexpression of NS1 suppressed miR-24 expression. Altogether, these findings suggest that the interaction between RSV NS1 and KLF6 modulates the expression of miR-24 and TGF-β, facilitating RSV replication [268]. Overexpression of miR-24 reversed PRRSV (porcine reproductive and respiratory syndrome virus) replication in MARC-145 cells and primary porcine alveolar macrophages [269]. During the life cycle of HP influenza A viruses, viral-specific repression of FURIN-directed miRs (e.g., miR-24) may express a new regulatory mechanism that dictates proteolytic stimulation of HA0 glycoproteins and the generation of infectious virions mediated by furin [270]. In A549 cells it has been demonstrated that RSV infection deregulates miR expression including miR-24 [271]. In infected epithelial cells or infected infant's nasal mucosa, miR-24, let-7f, let-7i, miR-31 and miR-221 are upregulated [272]. MiR-24 and miR-638 have also been reported as candidate antiviral host-encoded miRs that inhibit HBV replication [273]. The decrease in cellular miR-24 and miR-93 levels, which blocks VSV protein expression, is hyper susceptible to vesicular stomatitis virus (VSV)-mediated infection [274]. Human proprotein convertase subtilisin/kexin type 9 (PCSK9) is a predicted miR-24 target gene. The intricate interplay between circulating miR-24 and PCSK9 is an important player in lipid homeostasis and its regulation is affected by HCV infection and treatment-based viral cure [275].

Conclusion

Depending on the cell context, each miR regulates a plethora of biological processes and the pathophysiology of numerous diseases. Despite the availability of experimental data, we are still far from unravelling the biological pathways that are cross-regulated by miR-24. Based on the current knowledge, we systematically reviewed the distinct and context-dependent activities of both guide and passenger strands of miR-24 (miR-24, -24-1 and -24-2), highlighting its molecular targets, regulatory phenotypes and biological functions in various types of cancer and other human diseases to provide a theoretical understanding of miR-24 as a molecular target for diagnosis, prognosis and therapy. As described above, miR-24 contributes to several biological processes of carcinogenesis and the pathophysiology of several other diseases, drug resistance and so on. MiR-24 controls several key gene targets, including those are challenging in terms of druggability, which can further influence pleiotropic intracellular effects on multiple signal transduction pathways in a context-dependent manner. Currently, miR-based/targeted therapies are still in their infancy. Accumulating data strongly support the significance of miR-24 as an excel-

lent target for therapeutic usefulness; however to date, no miR-24-directed therapeutic strategy has been reported. This review will establish a molecular basis to lay the foundation for miR-24 in clinical applications in the future, highlighting its significance for targeted therapy. It is anticipated that future detailed research will provide more convincing support for further miR-24 directed diagnostic and prognostic tools and a brand-new insight to develop targeted therapeutics directed by miR-24.

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Disclosure of conflict of interest

None.

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