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Review Article

Dr. Jekyll or Mr. Hyde: The multifaceted roles of miR-145-5p in human health and disease

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ABSTRACT

MicroRNAs (miRNAs) are classified as small, non-coding RNAs that play crucial roles in diverse biological processes, including cellular development, differentiation, growth, and metabolism. MiRNAs regulate gene expression by recognizing complementary sequences within messenger RNA (mRNA) molecules. Recent studies have revealed that miR-145-5p functions as a tumor suppressor in several cancers, including lung, liver, and breast cancers. Notably, miR-145-5p plays a vital role in the pathophysiology underlying HIV and chronic obstructive pulmonary diseases associated with cigarette smoke. This miRNA is abundant in biofluids and shows potential as a biomarker for the diagnosis and prognosis of several infectious diseases, such as hepatitis B, tuberculosis, and influenza. Additionally, numerous studies have indicated that other non-coding RNAs, including long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), can regulate miR-145-5p. Given the significance of miR-145-5p, a comprehensive overview focusing on its roles in health and disease is essential. This review discusses the dual role of miR-145-5p as a protagonist and antagonist in important human diseases, with particular emphasis on disorders of the respiratory, digestive, nervous, reproductive, endocrine, and urinary systems.

1. Introduction

MicroRNAs (miRNAs) are small, single-stranded, non-coding RNAs that are endogenously produced and comprise 22–25 nucleotides [1,2]. These miRNAs play roles in post-transcriptional gene regulation in normal physiological and pathological conditions. miRNAs also play essential roles in numerous cellular processes, such as cell proliferation, differentiation, metabolism, apoptosis, development, and aging [3,4]. Additionally, miRNAs are also associated with the pathophysiology underlying numerous disorders, including oncogenesis, cardiovascular disorders, and neurological conditions [5]. The 3′-untranslated region (3′-UTR) of the open reading frame (ORF) serves as the primary binding site for most interactions between miRNAs and their target RNAs [6]. The specificity of miRNAs for their corresponding target sites is determined by a short seed sequence of 6–8 nucleotides located in the 3′-untranslated region (3′-UTR) of the target mRNA, and this interaction can lead to either translational repression or degradation of the mRNA [7,8]. Notably, miRNAs can function as either tumor suppressors or oncogenes, even though they are frequently downregulated in tumors compared to normal tissues [9]. Importantly, miRNAs are abundant in biological biofluids, highlighting their potential roles as noninvasive diagnostic and prognostic biomarkers for several human diseases. Moreover, a growing body of research indicates that exosomal miRNAs present in these biological fluids are crucial players in tumorigenesis [10]. Exosomes have an inherent ability to facilitate cargo delivery between cells and tissues, which effectively allows for the targeted incorporation of specific therapeutic miRNAs into these vesicles to target recipient cells [11,12]. Importantly, several studies have shown that other non-coding RNAs, such as lncRNAs and circRNAs, can modulate miRNA expression through different mechanisms [13–17]. Cytoplasmic

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long non-coding lncRNAs and circRNAs can serve as binding sites for specific miRNAs, functioning as miRNA sponges, and this activity provides an additional layer of regulation to miRNA-mediated post--transcriptional gene silencing, particularly in the context of tumor development [18,19].

MiR-145–5p is a microRNA that has been shown to play significant roles in various disorders. This particular miRNA is encoded by the MIR145 gene, which resides on Chromosome 5, specifically within the range of 149,430,646 to 149,430,733 on the forward strand [20]. The miR-145-5p has been considered a member of the p53 tumor suppressor family (Table 1) and is predominantly found in germline and mesoderm-derived tissues, including the heart, ovaries, prostate, spleen, testes, and uterus. Recent evidence has validated the impact of mRNAs in the pathogenesis of distinct cancerous and non-cancerous disorders [21,22]. Several studies have shown that miR-145-5p has the potential to regulate cell proliferation and migration by influencing diverse signaling pathways, including MAPK and PI3K/AKT [23,24]. Other findings have demonstrated the role of miR-145-5p in several pathologies, including respiratory disease, cancer, digestive, circulatory, and urinary system disorders (Fig. 1) [20,25,26]. Since miR-145-5p is expressed in a wide range of cells and its expression levels can manifest as upregulation or downregulation of genes involved in several human diseases (Tables 1 and 2), miR-145-5p exerts an important role as a disease modifier in multiple physiological and pathological processes. This review discusses recent studies focusing on miR-145-5p-target interactions and their downstream effects on pathways and pathophysiological processes in human disorders. Moreover, this review will enhance our understanding of the role of miR-145-5p in human diseases and assist in identifying new therapeutic avenues to alleviate alleviating the development and progression of conditions associated with abnormal miR-145-5p expression.

2. Biogenesis of miR-145-5p

MicroRNA (miRNA) expression and processing parallel the mechanism of small interfering RNA (siRNA)-mediated post-transcriptional gene silencing in plants, occurring through both canonical and non-canonical pathways, as illustrated in Fig. 2. Classical miRNAs are generated through the canonical pathway. Typically, miRNAs are transcribed in the nucleus by RNA polymerase II as primary miRNA (pri-miRNA) transcripts, which are several hundred nucleotides long and possess a hairpin-shaped structure, and these transcripts are initially modified with a 5′ cap and a 3′ poly(A) tail to enhance their stability and facilitate subsequent processing [27,28]. Primary miRNAs (pri-miRNAs) are processed into approximately 70-nucleotide (nt) long precursor miRNAs (pre-miRNAs) by the microprocessor complex, which consists of the RNAse III enzyme Drosha and its cofactor, DiGeorge syndrome critical gene 8 (DGCR8) [29]. In the next step, exportin-5 (Exp 5) exports pre-miRNA to the cytoplasm, which undergoes further processing into mature miRNA duplexes consisting of 20–25 nucleotides. This cleavage is carried out by the RNAse III endonuclease Dicer, along with its double-stranded RNA binding cofactor, the TAR RNA binding protein (TRBP) [30]. Two mature miRNAs are generated from the 5′, and 3′ arms and miR-145-5p and miR-145-3p are generated from the 5′ and 3′ arms of miR-145 (Fig. 2) [31]. Within the cytoplasm, the mature miRNA duplexes further undergo processing by DICER into two separate RNA strands known as the guide RNA strand (miRNA) and the passenger RNA. The RNA-induced silencing complex [32], which includes argonaute (Ago) proteins, becomes activated in the presence of miRNA and facilitates the targeting of the miRNA-induced silencing complex (miRISC) to target mRNA molecules [30,33,34]. The miRISC interacts with the 3′-UTR on its cognate mRNA targets, mediating gene silencing by either cleaving mRNA or inhibiting protein translation [34–37]. A seed sequence of 6–8 nucleotides is essential to mediate miRNA-based gene silencing. Thus, miRNA-mRNA interactions are promiscuous in that a single miRNA may regulate the expression of multiple genes, and a single gene can be regulated by multiple miRNAs [38]. Research has indicated that miRNAs can bind to the 5′ untranslated region (5′ UTR) [39] or directly to the ORF of target mRNAs [40]. However, targeting of the endogenous ORF appears to occur less frequently and effectively than the 3′ UTR, although it is still more common than targeting the 5′ UTR [36]. The inhibition of protein translation can be accomplished through several mechanisms, including the deadenylation of the poly(A) tail, competition between the Ago-RISC complex and translation initiation factors for the cap structure, interference with translation elongation, induction of premature ribosome dissociation, and degradation of the nascent polypeptide chain [41,42].

An alternative route in miRNA biogenesis, known as the non-canonical pathway, is associated with short introns referred to as mirtrons, which are capable of producing certain pre-miRNAs. This pathway has been identified in both invertebrates and mammals [43]. Initially, mirtron biogenesis uses spliceosomal machinery to initiate splicing and debranching into a pre-miRNA hairpin, which is typically short. This shorter hairpin structure is conducive to Dicer cleavage and is then integrated into RISC complexes [43–45]. These intron-derived miRNAs have been observed in cells from different species, including mammalian cells, signifying the evolutionary conservation of this miRNA-based regulation mechanism *in vivo* [46,47]. Some small nuclear RNAs have also been shown to act as sources of pre-miRNAs. In addition, miRNAs can also be derived from endogenous shRNAs and tRNA precursors [44]. Another pathway for miRNA biogenesis that is Dicer-independent has been recently identified in zebrafish and mammals [48]. In this pathway, specific miRNAs, such as miR-451, utilize the Argonaute protein-specifically Argonaute 2 (Ago2)-to facilitate their maturation. The process begins with Drosha, an enzyme in the microprocessor complex, which cleaves long pri-miRNAs into pre-miRNAs. These pre-miRNAs are then directly loaded into Ago2, which performs the critical final cleavage to produce the mature miRNA by removing the passenger strand. This unique mechanism highlights the versatility and adaptability of miRNA biogenesis. Notably, the Dicer-independent pathways allow for the maintenance of essential regulatory functions even in conditions where Dicer activity is diminished or absent, emphasizing their significance in vertebrate development and cellular responses [49,50].

The neighboring long non-coding RNA (lncRNA) CARMN plays a crucial role in the biogenesis of miR-145-5p by acting as a host gene that regulates its expression and processing [51]. CARMN is located adjacent to the miR-143/145 cluster, and its transcription is essential for the production of these microRNAs [52]. Specifically, miR-145-5p is

Table 1
The expression types of miR-145-5p in different human diseases.

System	Types of tumors	Expression level	Cell lines	References
Respiratory	Asthma	Up	16HBE	[80]
	NPC	Down	CNE, HNE-1	[57,145]
	NSCLC	Down	A549, NHBE	[94]
	LUAD	Up/Down	HEB, H1395	[146,147]
Digestive	HCC	Down	QSG7701, HL7702	[148]
	Esophageal cancer	Down	FLO-1	[149,150]
	Colorectal cancer	Down	HEK293	[151]
	Gastric cancer	Down	AGS	[152]
Other cancer	Breast cancer	Down	A459, MCF7	[149]
Reproductive	Cervical cancer	Down	C33A, HT-2, HeLa	[139]
	Ovarian cancer	Up	HEY, A2780	[153]
	Epithelial ovarian cancer	Down	SKOV-3	
	Prostate cancer	Down	22Rv1	[154]
Urinary	Bladder cancer	Down	SV-HUC-1	[155]
Endocrine	Pancreatic cancer	Down	MiaPaCa-2	[156,157]

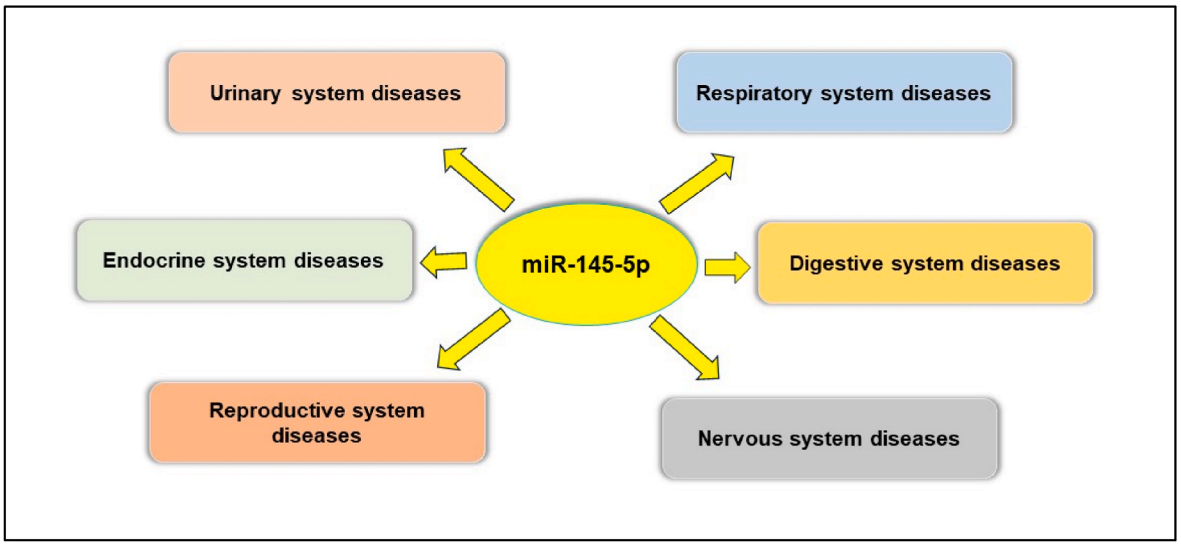

Fig. 1. Role of miR-145-5p in Diverse Pathologies: Insights into Respiratory, Digestive, Nervous, Reproductive, Endocrine, and Urinary Disorders.

embedded in the intronic region of the CARMN gene, which allows for co-expression of the lncRNA and the microRNA [52]. This arrangement facilitates the processing of miR-145-5p through mechanisms involving both transcriptional and post-transcriptional regulation [51]. Furthermore, CARMN influences the stability and availability of miR-145-5p by functioning as a competing endogenous RNA (ceRNA), which can modulate the levels of miR-145-5p′s target genes [53]. In addition, the sequence of miR-145 is highly conserved across species, including mammals and other vertebrates, indicating its fundamental role in biological processes [54]. This conservation underscores the importance of miR-145 in regulating gene expression and its potential as a therapeutic target across different biological contexts. MiR-145-5p primarily functions as a tumor suppressor across various cancer types, including bladder and colorectal cancers (CRC), by inhibiting cell proliferation, migration, and invasion [55]. Similarly, miR-145-3p is involved in distinct cellular processes such as proliferation, differentiation, and apoptosis [56,57]. It suppresses tumor development in multiple cancers by targeting oncogenes and inhibiting cancer cell growth [58]. Additionally, miR-145-3p is crucial in maintaining tissue homeostasis and facilitates the differentiation of smooth muscle cells, vascular remodeling, and the epithelial-mesenchymal transition [59,60]. Furthermore, it regulates stem cell pluripotency by targeting stem cell markers that are implicated in both normal development and tumor progression [61]. Fig. 2 illustrates the canonical and non-canonical pathways involved in miRNA biogenesis.

3. Structural features and biological characteristics of miR-145-5p

miR-145 is located on chromosome 5q32-33, spans 4.08 kilobases in length, and its sequence demonstrates a high degree of conservation compared to other non-coding small RNAs [62]. Comparative genomic analysis reveals that miR-145-5p exhibits significant sequence conservation across mammalian species, including humans, mice, and rats [54,63]. The high degree of conservation suggests that miR-145-5p plays a crucial regulatory role in various biological processes, including development, differentiation, and disease [64]. Conservation analysis indicates that the seed region (nucleotides 2–8), critical for target recognition, is remarkably well-preserved, highlighting the evolutionary importance of miR-145-5p′s gene regulatory functions across species [65]. MiR-145 locus generates pre-miR-145 and is processed to produce two mature miRNAs such as miR-145-5p and miR-145-3p (Fig. 3). The miR-145-3p transcript undergoes processing to generate miRNAs approximately 22 nts in length, while miR-145-5p produces fragments of 23 nucleotides. MiR-145 is located in a cluster near miR-143, and both transcripts are believed to have similar roles and are likely co-transcribed [66]. A study has shown that the chromosomal locus of miR-145, located near a critical tumor fragile site at 5q31, is involved in tumor generation; however, it is often removed in the chromosome rearrangements that occur during malignant transformation, contributing to the reduced expression levels of miR-145 in tumor tissues [67]. MiR-145 was initially identified in the heart of the experimental mouse models [68] and later observed in human CRC among other tissues [69]. Mesodermal tissues, including the uterus, ovary, testis, prostate, and heart, exhibit relatively high levels of miR-145. In contrast, this transcript (miR-145) shows relatively reduced expression in several tumor types, such as colon, breast, prostate, lung, liver, bladder, and ovarian cancers, as well as in pituitary adenomas and B-cell lymphomas [70]. Moreover, research indicates that miR-145 plays a protective role against tumorigenesis and can influence tumor growth, invasion, metastasis, and angiogenesis. This regulation occurs through either complete or partial binding to the 3′ non-coding region of target mRNAs, leading to their degradation and impacting their translation levels [62].

3.1. *MiR-145-5p in health and disease*

3.1.1. *MiR-145-5p in pulmonary diseases*

3.1.1.1. Asthma. Asthma is a chronic respiratory disease in which the airways become narrow and swollen, leading to difficulty breathing, coughing, wheezing, and chest tightness. It is estimated to affect 334 million individuals worldwide [71,72]. Asthma is prevalent in developing countries and contributes to poor quality of life and economic burdens worldwide. While several treatment regimens are available, the prognosis of asthma remains poor [73]. Recent advances demonstrate the involvement of numerous small non-coding RNAs, including miRNAs, in asthma. Specifically, miR-145-5p is identified as an important modifier of disease in asthma and presents itself as a promising target for therapeutic interventions to restore normal levels of miR-145-5p expression. Clinical studies have demonstrated that patients with asthma exhibit elevated plasma levels of miR-145-5p in comparison to healthy control subjects [74]. Furthermore, increased miRNA levels are associated with a higher eosinophil count in the blood [75]. A cross-sectional study involving children with various asthma phenotypes indicated that the levels of miR-145-5p in exhaled breath condensate have a positive correlation with asthma severity [76]. Tiwari

Table 2
Potential roles of miR-145-5p in different human diseases.

System	Type of diseases	Target Genes	Functions	References
Respiratory	Asthma	RUNX3 KIF3A	Regulates the balance of Th1/Th2 suppressed epithelial repair	[80]
	NPC	KLF5	Regulate the activity FAK, downregulate the proliferation, migration, and invasion of NPC	[105]
	NPC	NUAK1, p-AKT	SNHG1, by the miR-145-5p/NUAK1 axis, could enhance cell aggressiveness by targeting the AKT pathway and inducing EMT.	[104]
	NSCLC	MAP3K1	inhibits EMT via the JNK signaling pathway	[158]
	NSCLC	FGF5	miR-145–5p/FGF5 is being regulated via circ 0016760, promotes cell proliferation	
	NSCLC	Sp1	Regulates cell proliferation via FKBP3	[159]
	NSCLC	TP53	miR-145-5p acts as an inducer of SOX2 expression in NSCLC.	[90]
	NSCLC	CXCL3	CXCL3/miR-145-5p augments the proliferation of NSCLC cells via CircMET	[95]
Digestive	HCC	GOLM1	miR-145/mTOR axis regulate GOLM1 that result the exacerbation of HCC	[109]
	HCC	ARF6	Negatively regulates cell proliferation, promote apoptosis	[160]
	HCC	NRAS	Enhance HCC cells proliferation	136]
	HCC	CDCA3	Promote proliferation and invasion the affected cells	[161]
Circulatory	Atherosclerosis	CaMKII	Involved in cardiac remodeling	[162]
Urinary	CGN	CXCL16	miR-145-5p inhibits the AKT/GSK pathway and diminished the expression of inflammation-associated miRNAs	[127]
	DKD	Srgap2	miR-145-5p mediates podocyte apoptosis	[129]
	BC	TGFBR2	Inhibition of BC cells proliferation and migration	[163]
Other cancer	BC	SOX2	Inhibition of BC cells proliferation	[164]
	BC	Ago2	miR-145-5p restoration results Ago2 induction and cell migration inhibition	[155]
	BC	H2AFX	Inhibits Malignant Behaviors of BC cells	[165]
	BC	PD-L1	Initiates apoptosis, cell cycle arrest in BC cells	[166]
Reproductive	PC	PLD5	Repressed PC cell migration, invasion, and metastasis	[136]
	CC	KLF5	Inhibits cervical cancer cell proliferation	[139]
	CC	FSCN1	Suppress tumor of cervical cancer	[140]
	CC	WNT2B	Inhibits cancer cell progression and metastasis	[141]
	EOC	SMAD4	Promotes EOC cells death	[142]
Nervus	PD	Nurr1	Reduce infarct volume in acute cerebral ischemia	[167]
	AD	Smad4	inhibits VSMCs proliferation and migration	[168]

and colleagues showed that children with asthma (reduced growth and early decline) who showed lower FEV1 values (reduced growth and early decline) demonstrated a high reduction of miR-145-5p levels in plasma compared with children with only reduced growth or children with normal growth [77]. Additionally, children with early decline demonstrated elevated miR-145-5p levels compared to those with reduced growth [77]. The study further showed that the children with asthma who ended follow-up were affected by COPD and manifested a substantial decrease in plasma miR-145-5p levels compared to those who were not affected by COPD [77]. Another subsequent study showed the correlation between miR-145-5p dysregulation and the impaired patterns of lung function that contribute to the development of COPD in children with asthma [77]. The development of asthma has been associated with the presence of certain genetic variants in the miR-145 gene [25]. These variants may significantly influence the risk of developing this chronic respiratory condition [78].

Research utilizing experimental asthma models has investigated the involvement of miR-145-5p in the development of asthma. In mouse models of asthma triggered by exposure to house dust mite (HDM), there was a notable increase in the expression of miR-145-5p within the airway walls [79]. The same study indicated that inhibiting miR-145-5p in asthmatic mice led to a marked decrease in airway hyperresponsiveness, which was associated with a reduction in both mucus-producing cells and eosinophils in the airways. This decrease was attributed to lower production of IL-15 and IL-13 from antigen-specific Th2 cells [79]. A study conducted by Xiong and colleagues on a mouse model of asthma caused by house dust mite (HDM) exposure demonstrated an up-regulation of miR-145-5p expression, along with a down-regulation of kinesin Family Member 3A (KIF3A) levels in airway epithelial cells (Fig. 4A) [80]. In contrast, Cheng and colleagues conducted a study to determine how miR-145-5p influences airway remodeling and cytokine expression by targeting epidermal growth factor receptor (EGFR) to modulate mucin 5AC (MUC5AC) using an ovalbumin (OVA)-induced asthmatic mouse model. The research findings indicate that the expression of miR-145-5p promotes reduced airway remodeling by controlling EGFR levels, in comparison to asthmatic mice in which miR-145-5p expression is inhibited [81]. Similarly, the negative regulation of EGFR by miR-145-5p resulted in a decrease in

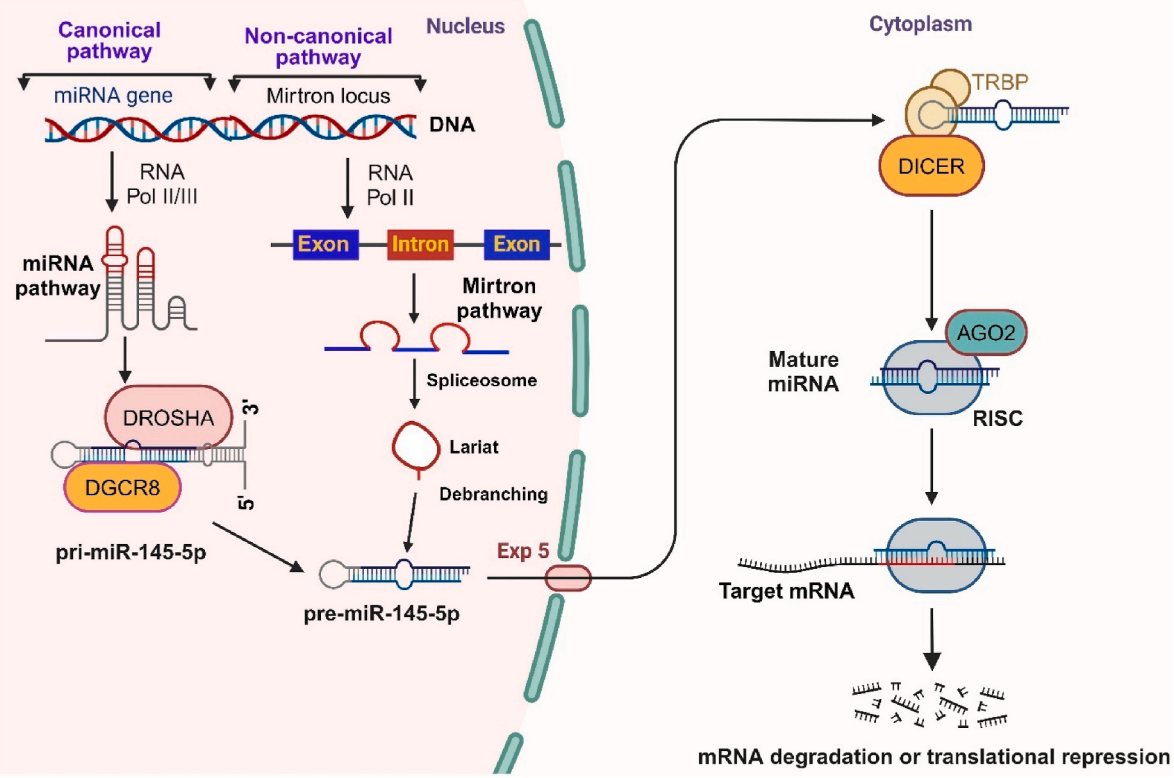

Fig. 2. The biogenesis of miRNAs can occur through canonical and noncanonical pathways. In the canonical pathway, primary miRNA (pri-miRNA) transcripts are produced from miRNA genes by RNA Polymerase II or III (RNA pol II/III). These pri-miRNAs are then processed into precursor miRNAs (pre-miRNAs) by the Drosha-DGCR8 complex. In contrast, the noncanonical pathway involves the formation of intronic pre-miRNA hairpins, which are transcribed by RNA Polymerase II. This process includes splicing, debranching, and trimming of short introns (lariat), bypassing the Drosha processing step. The pre-miRNAs generated from both pathways are exported from the nucleus through exportin-5 (Exp 5). Subsequently, Dicer, along with TRBP, processes them into double-stranded RNAs known as mature miRNA duplex. Argonaute (Ago) proteins then unwind these double-stranded RNAs, separating the guide strand (miRNA) from the passenger strand. The mature miRNA is incorporated into the RNA-induced silencing complex [32], which interacts with the 3′ untranslated region (3′ UTR) of target mRNAs to regulate gene expression, primarily through translation inhibition or mRNA degradation.

the levels of both Th2 and Th17 cells in the blood, as well as a reduction in inflammatory factors in asthmatic mice. This effect was notable when compared to asthmatic mice that had inhibited miR-145-5p expression [81].

Molecular-level analysis in cells from asthma models has also provided promising evidence for the role of miR-145-5p in the development of asthma. Human airway smooth muscle (ASM) cells treated with TNF-α, IL-1β, and IFN-γ demonstrated significant upregulation of miR-145-5p and downregulation of Krüppel-like factor 4 (KLF4) [82]. The same study revealed that the overexpression of miR-145-5p, which negatively regulates KLF4, led to increased proliferation and migration of ASM cells *in vitro*. This finding suggests that miR-145-5p may play a role in the smooth muscle remodeling associated with asthma pathology (Fig. 4A) [82]. Furthermore, Qiu Yu-Ying and colleagues observed that $CD4^+$ T cells from asthma patients exhibited elevated levels of miR-145-5p and reduced expression of Runt-related transcription factor 3 (RUNX3) compared to healthy controls [83]. Fan Linxia and colleagues demonstrated that $CD4^+$ T cells from asthma patients displayed increased expression of both miR-145-5p and IL-4 (a Th2 marker) while showing decreased levels of IFN-γ (a Th1 marker) and RUNX3 [84]. Inhibiting miR-145-5p in $CD4^+$ T cells from asthma patients resulted in an increased proportion of IFN-γ+ $CD4^+$ T cells through the regulation of RUNX3. This indicates that miR-145-5p plays a role in modulating the Th1/Th2 balance in asthma (Fig. 4B). Consequently, the numerous evidence points to miR-145-5p as a significant miRNA involved in the progression of asthma by influencing the Th1/Th2 balance and contributing to airway remodeling. Surprisingly, no clinical trials to date have focused on regulating miR-145-5p for the treatment of asthma.

3.1.1.2. Lung cancer. Lung cancer remains the most frequently diagnosed cancer and the foremost cause of cancer-related mortality worldwide. As reported by GLOBOCAN in 2020, there were approximately 2.2 million new cases of lung cancer, accounting for 11.4 % of all cancer diagnoses and nearly 1.8 million deaths, making up 18.0 % of all cancer-related fatalities during that year [86]. Lung cancer can be categorized into two main groups, namely non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), in which NSCLC is more prevalent and constitutes 85 % of cases [87]. Chest discomfort, shortness of breath, coughing, and weight loss are typical symptoms of lung cancer [88]. A comprehensive study conducted by Gan and colleagues, utilizing a total of 125 paired clinical samples from patients with NSCLC, has provided a thorough investigation. The study measured the level of miR-145-5p and its association with clinicopathological parameters, confirming that the expression of miR-145-5p in NSCLC is significantly lower compared to normal healthy tissue [89]. In 2016, Erdem and coworkers examined the relationship between TP53 mutational status and the variation in SOX2 copy number and gene expression in patients with early-stage NSCLC. *In vitro* experiments indicated reduced TP53 expression corresponded with a decrease in SOX2 expression. Thus, the TP53 signaling pathway could play a crucial role in modulating the copy number and expression of SOX2 in NSCLC tumors, with the miR-145-5p potentially serving as a critical regulator [90]. The protein-protein interaction network analysis shows that eight hub genes in NSCLC act as potential target genes of miR-145-5p [89]. Lu and colleagues identified a lncRNA known as small nucleolar RNA host gene 1 (SNHG1), which has emerged as a novel lncRNA elevated in various types of human cancers. In NSCLC tissue and cells, SNHG1 is significantly

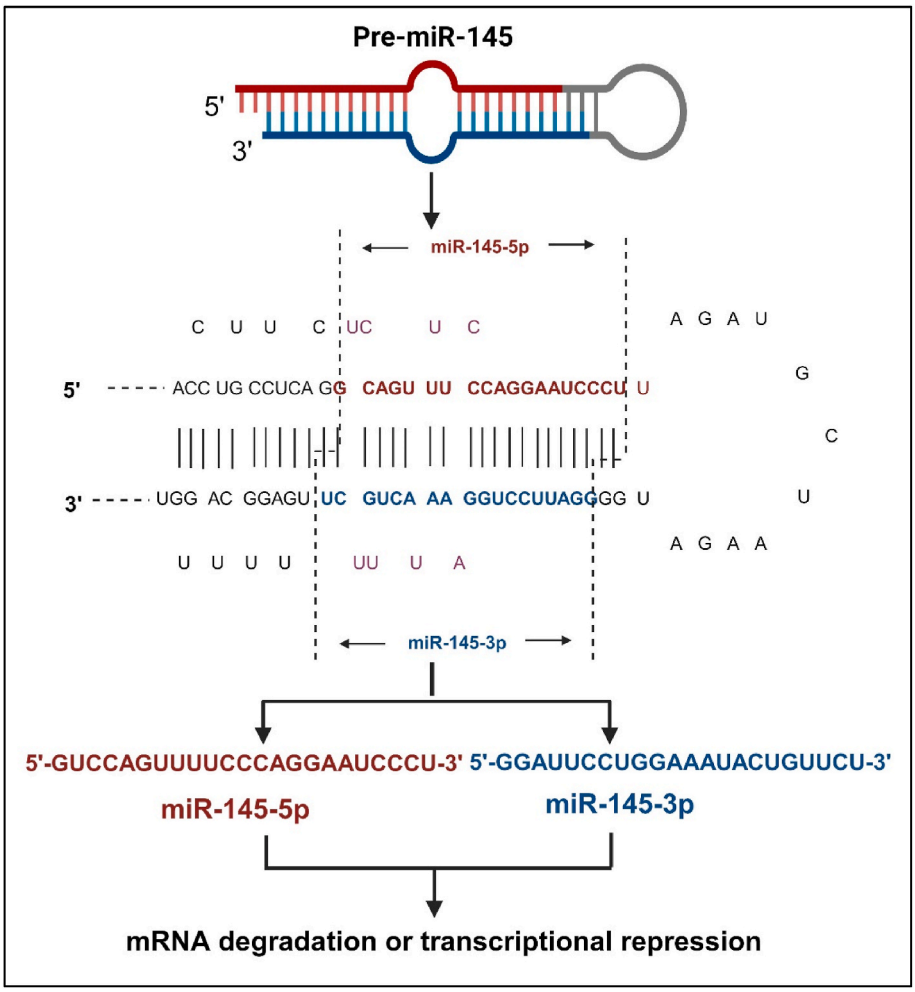

Fig. 3. The structure of pre-miR-145. Two mature miRNAs, miR-145-5p and miR-145-3p, are generated from the 5′ and 3′ arms of the pre-miR-145 structure.

upregulated. Furthermore, the silencing of SNHG1 leads to a reduction in tumor volumes. In addition, the investigation of the regulatory mechanism demonstrated that SNHG directly interacts with miR-145-5p, thereby sequestering miR-145-5p from its target gene, MTDH. Suppressing SNHG1 led to reduced proliferation and invasion of NSCLC cells *in vitro*. The inhibition of SNHG1 resulted in a decrease in NSCLC cell viability, proliferation, migration, and invasion *in vitro*; however, these effects were reversed by the inhibition of miR-145-5p. These findings indicate that SNHG1 plays a role in the progression of NSCLC by regulating miR-145-5p/MTDH axis [91]. Li and group analyzed the impacts of TNF-α in NSCLC, and it can induce expression of several genes such as TNF-α-induced protein 2 (TNFAIP2) in NSCLC and evidenced that TNFAIP2 has a crucial role in NSCLC progression, and its epigenetic regulation mediated by miR-145-5p. Western blot, immunohistochemistry, and RT-qPCR were used to validate the TNFAIP2 expression in NSCLC tissue. All *in vitro* assays were conducted using A549 and H23 cells, while chemoresistance assays were performed on the A549/Cisplatin and H23/DDP cell types. Silencing of TNFAIP2 was achieved by introducing specific siRNA through lipofectamine transfection. In addition, cells were co-transfected with miR-145-5p along with either the TNFAIP2-3′ UTR or a mutated TNFAIP2, utilizing the pGL luciferase vector. The involvement of the Caspase 3 protein in cell viability was determined through Western blot analysis. The tumor tissues and the cisplatin-resistant cell lines A549/DDP and H23/DDP exhibited markedly elevated levels of TNFAIP2 mRNA expression. In A549/DDP and H23/DDP cell lines, the silencing of TNFAIP2 decreased cell viability and enhanced induction of caspase 3. The overexpression of miR-145-5p led to the reduction of TNFAIP2 expression, reduced cell viability, inhibited cell migration and invasion, and notably decreased caspase 3 protein expression [92]. The progression of NSCLC is influenced by the regulatory functions of circular RNA (circRNAs) [93]. The expression of hsa_circ_0016760 has been reported to be increased in NSCLC. Hsa_circ_0016760 enhanced the expression of FGF5 by sponging miR-145-5p. The upregulation of miR-145-5p or downregulation of FGF5 reversed the stimulatory effects of hsa_circ_0016760 on the proliferation, migration, and invasion of NSCLC cells *in vitro* [94]. Pei and collaborators uncovered the involvement of a circular RNA (circMET) in NSCLC and found that circMET functions as a sponge for miR-145-5p, leading to the upregulation of CXCL3 expression [95]. MiR-145-5p can influence gene regulation indirectly by modulating the expression of other non-coding RNAs, especially lncRNAs. For instance, miR-145-5p can regulate gene expression by directly binding to lncRNA [96]. Wei and colleagues evaluated the roles of lncRNA plasmacytoma variant translocation 1 (PVT1) in regulating NSCLC cell proliferation. RT-qPCR confirmed the elevated PVT1 and integrin-β-8 (ITB8) expression in NSCLC tissues and cell lines. The knockdown of either PVT1 or ITGB8 inhibited cell proliferation while promoting apoptosis in NSCLC cells, an effect reversed by the overexpression of ITGB8. Furthermore, PVT1 was found to regulate ITGB8 expression by directly binding to miR-145-5p [97]. Zheng and colleagues demonstrated that circPVT1 acted as a competing endogenous RNA to inhibit miR-145-5p in A549 cells that exhibit resistance to cisplatin and pemetrexed [98]. Pemetrexed is a folic acid inhibitor and a well-used drug in the treatment of NSCLC, and its prolonged treatment led to cancer cells gaining resistance. Chang and

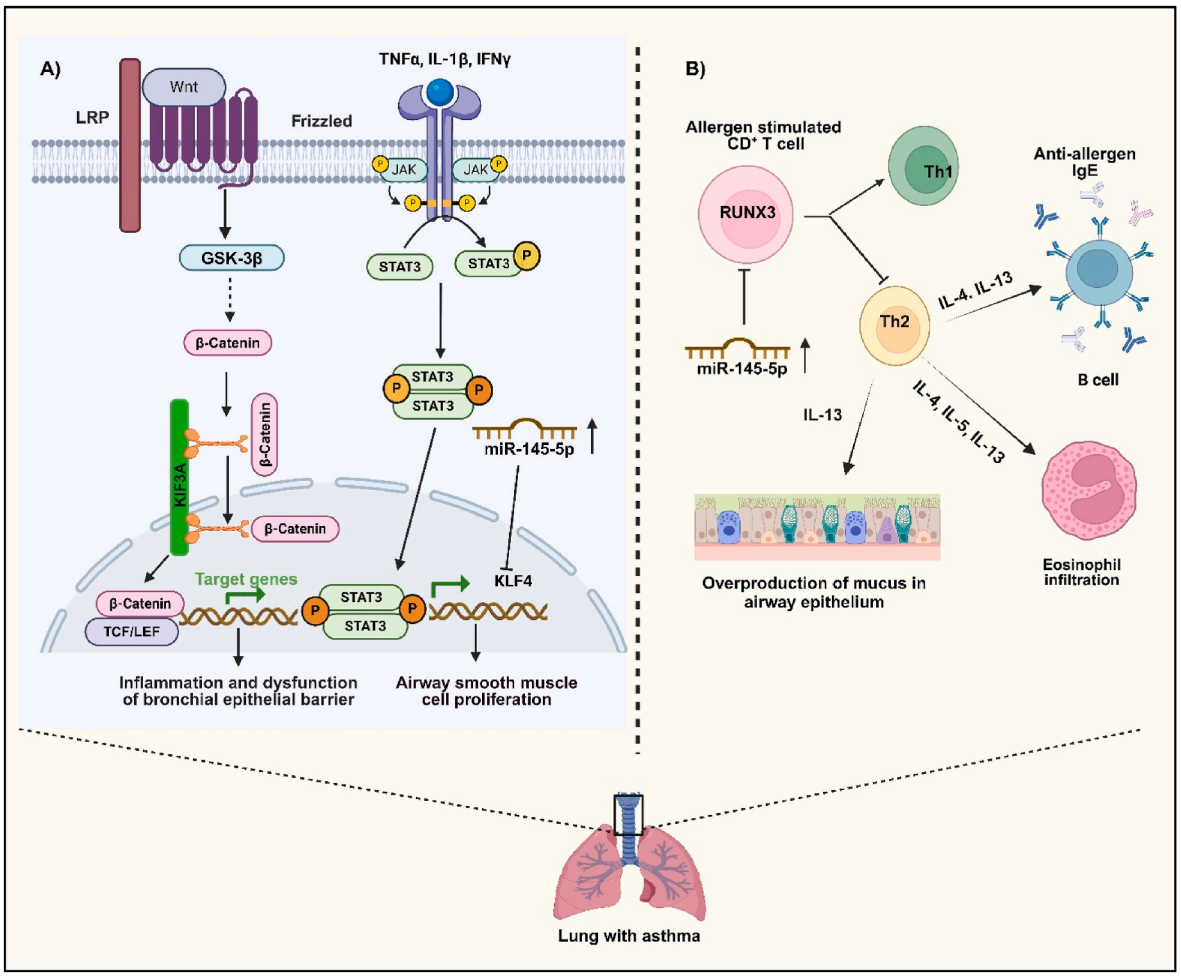

Fig. 4. Potential roles of miR-145-5p in the development of asthma. This figure has been redrawn from Ref. [85]. **A)** The expression of miR-145-5p in asthma is associated with the disruption of Wnt/β-catenin and cytokine signaling pathways. This disruption contributes to inflammation, bronchial epithelial dysfunction, and the proliferation of airway smooth muscle. **B)** miR-145-5p promotes the differentiation of Th2 cells and contributes to the manifestation of the Th2 phenotype. Variations in miR-145-5p levels, whether up-regulated or down-regulated, lead to alterations in RUNX3 expression in $CD4^+$ T cells, which in turn affects cytokine levels. Inhibiting miR-145 may restore the Th1/Th2 balance that is often disrupted in asthma.

colleagues investigated the role of miR-145-5p in pemetrexed-resistant cells and observed that the expression levels of BMI1 (B Lymphoma Mo-MLV insertion region 1 homolog) and Sp1 were elevated in pemetrexed-resistant A400 cells compared to A549 cells, while the expression of miR-145-5p is notably reduced. Altered expression of miR-145-5p in A400 or A549 cells through the transfection of either a miR-145-5p mimic or an inhibitor influences the cell's sensitivity to pemetrexed. Furthermore, the overexpression of BMI1 in A549 cells led to an increase in Sp1 levels and a reduction in miR-145-5p, which was associated with increased cell proliferation and elevated expression of EMT. These effects could be diminished through the overexpression of miR-145-5p or by treating mithramycin, an inhibitor of Sp1. Conversely, increased expression of Sp1 in A549 cells led to reduced sensitivity to pemetrexed, enhanced the cells' migratory abilities, and upregulated EMT-related transcription factors, including Snail Family Transcriptional Repressor 1 (Snail 1) and Zinc Finger E-Box Binding Homeobox 1 (ZEB1). These findings indicate that BMI1 overexpression leads to the downregulation of miR-145-5p, which subsequently enhances Sp1 expression and promotes the EMT process in pemetrexed-resistant NSCLC cells (Fig. 5) [99].

3.1.1.3. Nasopharyngeal carcinoma. Nasopharyngeal carcinoma (NPC) is one of the predominant malignancies of the head and neck region in humans [100]. It is considered a major health concern in low-income countries and has an uneven geographic distribution, with Southeastern Asia being one of the most affected regions. In 2020, it was estimated that around 133,354 cases of NPC occurred worldwide, leading to approximately 80,008 [101] deaths, with 129,000 new cases of NPC in 2018 [102]. Chen and colleagues demonstrated an important association of NPC pathogenesis with Epstein-Barr virus (EBV) infection [102]. Plasma Epstein-Barr virus (EBV) DNA has been utilized for various purposes, including population screening, prognostic assessment, predicting responses to treatment for therapeutic adjustment, and monitoring disease progression [102]. Thirteen nasopharyngeal carcinoma (NPC) tissue samples were analyzed to evaluate miRNAs' expression using stem-loop real-time PCR, revealing that thirty-five miRNAs were dysregulated, including a significant suppression of miR-145-5p [103]. In another study, Lan and colleagues investigated how lncRNA SNHG1 enhances the aggressiveness of NPC cells by utilizing a dual luciferase reporter assay to explore the potential relationship between SNHG1, miR-145-5p, and NUAK1. LncRNA SNHG1 enhanced the expression of NUAK1 by inhibiting miR-145-5p, thereby increasing the aggressiveness of NPC cells through the AKT signaling pathway and facilitating EMT [104]. A more recent study in 2022 reported that miR-145-5p is capable of reducing both the mRNA and protein levels of KLF5 in NPC cell lines. Moreover, miR-145-5p and KLF5 were found to regulate focal adhesion kinase activity, which serves as a marker for cell migration in NPC cells [105].

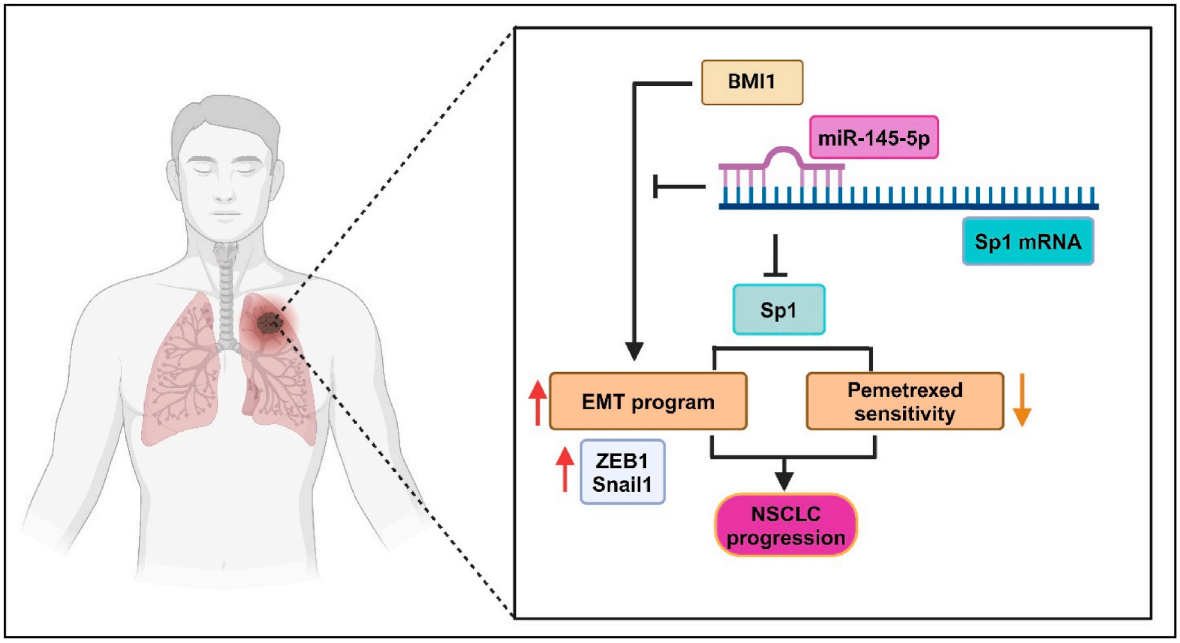

Fig. 5. Regulatory roles of miR-145-5p in pemetrexed-resistant in NSCLC. This figure has been redrawn from Ref. [99]. Prolonged treatment with chemotherapeutic agents such as pemetrexed can lead to the development of resistance in cancer cells. In this context, Sp1 is overexpressed, resulting in reduced sensitivity to pemetrexed, increased cell migration, and the upregulation of epithelial-mesenchymal transition (EMT)-related factors such as Snail and ZEB in A549 cells. Furthermore, the overexpression of BMI1 contributes to the upregulation of Sp1, which in turn suppresses the expression of miR-145-5p. This suppression promotes enhanced cell proliferation and elevates the levels of EMT-related transcription factors. However, these detrimental effects can be mitigated either by increasing the expression of miR-145-5p or by employing treatments that inhibit Sp1 activity.

4. Disease of the digestive system

4.1. Hepatic disorders

Recent research has highlighted the importance of miR-145-5p in hepatic disorders, particularly in hepatocellular carcinoma (HCC). A growing body of research indicates that miR-145-5p functions as a tumor suppressor in HCC and is notably suppressed in various molecular subtypes of the disease [106,107]. A reduced expression level of miR-145-5p was significantly linked to poor prognosis in patients with HCC [108]. *In vitro* studies demonstrated that miR-145-5p inhibited cell proliferation, migration, and invasion while promoting apoptosis in HCCLM3 cells [108]. Recent research has shown that miR-145 suppresses cell migration and invasion, potentially by targeting Golgi membrane protein 1 (GOLM1), although the impacts of miRNAs in HCC remain fully elucidated [109]. ADP-ribosylation factor 6 (ARF6), a member of the ARF family that is involved in various cellular processes, plays a crucial role in hepatocellular HCC, and it has been reported that miR-145-5p suppresses ARF6, thereby inhibiting HCC cell migration and invasion, while restoring ARF6 expression abolishes the inhibitory effects of miR-145-5p, highlighting the importance of their interaction [109–111]. Recent research has underscored the significance of numerous protein-coding and non-coding genes, such as microRNAs, including miR-145, in initiating and advancing liver cancer. The expression level of miR-145 was significantly reduced in hepatic cancer cell lines and cancerous liver tissues. Restoring miR-145 levels was shown to decrease migration and invasion capabilities, as well as inhibit the proliferation in various cell lines, including HepG2 and Hep3B [112].

4.2. Gastrointestinal diseases

According to the study conducted by He and colleagues on gastric cancer, lncRNA MACC1-AS1 plays a critical role in promoting fatty acid oxidation (FAO), which is associated with stemness and chemoresistance. This process occurs through the targeting of miR-145–5p. Conversely, miR-145–5p has been shown to mitigate the suppressive effect of MACC1-AS1 on cellular sensitivity to chemotherapy agents such as 5-FU and oxaliplatin. Furthermore, miR-145–5p enhances reactive oxygen species (ROS) production and leads to increased cell death [113]. Another study has demonstrated that when liver cancer cells were cultured in low glucose conditions, miR-145-5p was found to decrease the expression of miR-483-3p, which promoted apoptosis. In contrast, under high glucose conditions, the levels of miR-483-3p rose, leading to a reduced rate of apoptosis. This observation suggests that the effect of miR-145-5p on miR-483-3p varies with glucose availability, exhibiting both inhibitory and stimulatory characteristics [114]. Kadhoda and colleagues have demonstrated that miR-145-5p potentially plays a role in combating various cancers, including bladder, breast, cervical, renal, and gastrointestinal cancers, as well as in non-cancerous conditions such as aplastic anemia, asthma, reperfusion injury, and diabetic neuropathy. Future studies should focus on the development of innovative delivery methods for targeted therapies, aiming to enhance both their effectiveness and safety [20]. MiR-145 is frequently downregulated in CRC tissues and cell lines. This downregulation is correlated with aggressive tumor phenotypes and worse clinical outcomes, indicating its role in suppressing tumor progression [115]. Researchers have noted that reduced levels of miR-145 may lead to enhanced invasive and metastatic capabilities of CRC cells, contributing to the disease's severity [116]. MiR-145-5p targets various oncogenes and signaling pathways, including the c-MYC and p70S6K1, to suppress tumor cell growth and induce apoptosis [117]. Additionally, it directly influences epithelial-mesenchymal transition (EMT) through the regulation of genes such as Fascin-1 and N-cadherin, which are crucial for maintaining the invasive characteristics of cancer cells [116].

5. Cardiovascular diseases

Cardiovascular diseases (CVDs) are an umbrella term that includes a group of disorders of the heart and blood vessels. CVDs can be classified

into four major groups, namely coronary artery disease [70], cardiovascular disease, peripheral artery disease, and aortic atherosclerosis [118]. World Health Organization reports that cardiovascular disease was the leading cause of global mortality in 2021, and an estimated 17.9 million individuals are affected by CVDs [119]. Numerous studies highlight the importance of miR-145 as a crucial modulator in cardiovascular diseases (CVDs). Boettger and colleagues have shown that miR-145-5p is an essential regulator of the contractile phenotype in vascular smooth muscle cells (VSMCs), which plays a significant role in various CVDs, including arteriosclerosis. This finding suggests that miR-145-5p has the potential to be utilized as a diagnostic biomarker for this condition [120]. Recently, Kontaraki and colleagues observed that the expression levels of miR-143/-145 in human peripheral blood mononuclear cells (PBMCs) were reduced in patients with hypertension compared to healthy control individuals [121]. Angiotensin-converting enzyme (ACE) is regulated by miR-145, where the downregulation of miR-145 leads to increased ACE expression, thereby enhancing the renin-angiotensin system's activity and contributing to the maintenance of hypertension [122,123]. Furthermore, Liu and coworkers have shown that miR-145 plays a crucial role in alleviating heart failure-related cardiac remodeling by enhancing cardiac dilation, reducing fibrosis, addressing intracellular Ca^{2+} mishandling, and stabilizing electrophysiological function [124]. MiR-145-5p plays a significant role in the pathogenesis of Chagas disease by modulating the immune response and influencing parasite load in infected cardiomyoblasts. The microRNA miR-145-5p plays a pivotal role in Chagas disease, particularly in the context of *Trypanosoma cruzi* infection within H9C2 rat cardiomyoblast cells. Farani and colleagues have demonstrated that higher levels of miR-145-5p correlate with reduced parasite load in H9C2 cardiomyoblasts infected with *Trypanosoma cruzi*, suggesting that miR-145-5p may serve as a potential therapeutic target or biomarker for monitoring disease progression and treatment in patients with chronic Chagas disease [32]. These collective findings emphasize the diverse roles of miR-145 on cardiovascular health and posit its therapeutic potential in mitigating CVDs and related complications.

6. Diseases of the renal system

Alterations in miRNA expression can interfere with the early stages of kidney development and have been associated with the onset of kidney disease [125]. The increased level of urinary exosomal miR-145-5p has been associated with the progression of chronic kidney diseases. Furthermore, research indicates that the inhibition of miR-145-5p is associated with necrosis in HK-2 cells *in vitro* [126]. Wu and coworkers explored the role of miR-145-5p in regulating the proliferation and inflammatory responses of renal mesangial cells and showed that miR-145-5p reduced the expression of CXCL16 protein by binding to its 3′-UTR, which in turn inhibited the AKT/GSK signaling pathway and led to a decrease in the levels of mRNAs related to inflammation [127]. A subsequent study revealed that urinary exosomal miR-145-5p levels were significantly elevated in patients with diabetic kidney disease (DKD) and were associated with the advancement of kidney injury in individuals with type 2 diabetes mellitus (T2DM) [128]. Han and colleagues investigated the mechanism of podocyte apoptosis employing urinary exosomes obtained from T2DM and DKD patients and summarized that urinary exosomal miR-145-5p plays crucial roles in mediating podocyte apoptosis by inhibiting Srgap2 and activating the RhoA/ROCK pathway [129]. Chen and colleagues explored the therapeutic effects of Salvianolic acid B (SalB) on mesangial cell abnormalities caused by membranous nephropathy (MN) to understand the underlying mechanisms. They created experimental models of MN by administering bovine serum albumin to Dawley rats and treating human mesangial cells (HMCs) with lipopolysaccharide. After 24 h of treatment with SalB and a miR-145-5p inhibitor, they evaluated kidney function by measuring urine protein, serum creatinine, and blood urea nitrogen levels. The results demonstrated that SalB improved kidney function, reduced cell proliferation, and promoted autophagy in mesangial cells. Conversely, the use of the miR-145-5p inhibitor led to increased proliferation and inflammation in HMCs through the activation of the PI3K/AKT signaling pathway. Overall, the study illustrated that SalB facilitates renal autophagy, thereby reducing cell proliferation and inflammation related to MN, a process mediated by miR-145-5p, which inhibits the PI3K/AKT pathway and contributes to the attenuation of MN [130].

7. Diseases of the reproductive system

Prostate cancer is a major health concern due to its high morbidity and mortality [86,131]. Each year, 1.3 million cases are reported worldwide, resulting in 400,000 deaths from metastatic prostate cancer. The skeletal system, particularly the bones, is the primary site for prostate cancer metastasis, leading to severe skeletal manifestations such as bone pain [132]. MiR-145-5p dysregulation is also prevalent in cervical, ovarian, and prostate malignancies [133]. The overexpression of miR-145-5p suppresses the proliferation of prostate cancer cells and leads to a decrease in SOX2 expression [134].

WIP1, or wild-type p53-induced phosphatase 1, is a proto-oncogene that is frequently overexpressed in prostate cancer [135]. Bioinformatics analysis has shown that miR-145-5p can target WIP1, which is also validated by a dual-luciferase experiment. Downregulation of WIP1 is associated with the inhibition of prostate cancer cell proliferation, while overexpression of WIP1 reverses the anticancer effect of miR-145-5p [135]. The anticancer effects of miR-145 were achieved through the inhibition of the PI3K/AKT signaling pathway and the upregulation of ChK2 and p-p38MAPK. Collectively, these findings demonstrate that miR-145-5p suppresses the growth and metastasis of PC cells by downregulating the proto-oncogene WIP1, thus exerting tumor-suppressive functions in prostate cancer [135]. Another study exhibited that miR-145-5p downregulates Phospholipase D5 (PLD5), leading to a reduction in cell proliferation and metastasis, which helps alleviate prostate cancer progression [136]. Luo and colleagues explored the effect of miR-145-5p on the development and progression of prostate cancer. MiR-145-5p plays a significant role in inhibiting bone metastasis in PC cells by negatively regulating epithelial-mesenchymal transition (EMT) processes, which are crucial for cancer invasion and migration [137]. Specifically, it influences the expression of several key proteins, including E-cadherin, which is vital for maintaining cell adhesion [137]. MiR-145-5p enhanced the expression of the epithelial marker E-cadherin while decreasing matrix metalloproteinase 2 and 9 (MMP-2 and MMP-9) [138]. Moreover, miR-145-5p promotes apoptosis in PC cells by enhancing the expression of caspase 9, which is a critical mediator in the apoptotic pathway. Therefore, the modulation of these factors by miR-145-5p contributes to its tumor-suppressive functions in bone metastasis (Fig. 6B) [137].

In cervical cancer (CC), the expression of miR-145-5p was downregulated, and KLF5 was upregulated in both CC tissue and cells. Cao and colleagues analyzed the role of miR-145-5p on KLF5 using C33A, HT-2, and HeLa cell lines. The KLF5 3′-UTR contains a seed sequence for miR-145-5p, and miR-145-5p downregulates KLF5, subsequently inhibiting proliferation, migration, and invasion of CC cells [139]. Another study was conducted by He and the group to explore the role of miR-145-5p in CC using HeLa cell lines and demonstrated its relationship with fascin (FSCN1). HeLa and ECT1/E6E7 cells were transfected with FSCN1 or with mimics and inhibitors to figure out the cancer cell's viability, migration, and invasion by employing the cell counting kit-8 and Transwell assays. FSCN1 mRNA and protein expression were evaluated by reverse transcription PCR and Western blot analysis. There was a significant reduction in the expression levels of miR-145-5p in cervical cancer (CC) tissues and cell lines, while FSCN1 levels were notably elevated in these same tissues and cells. Nonetheless, the overexpression of miR-145-5p led to decreased invasion, migration, and viability of HeLa and ECT1/E6E7 cells. Similarly, reducing FSCN1 expression

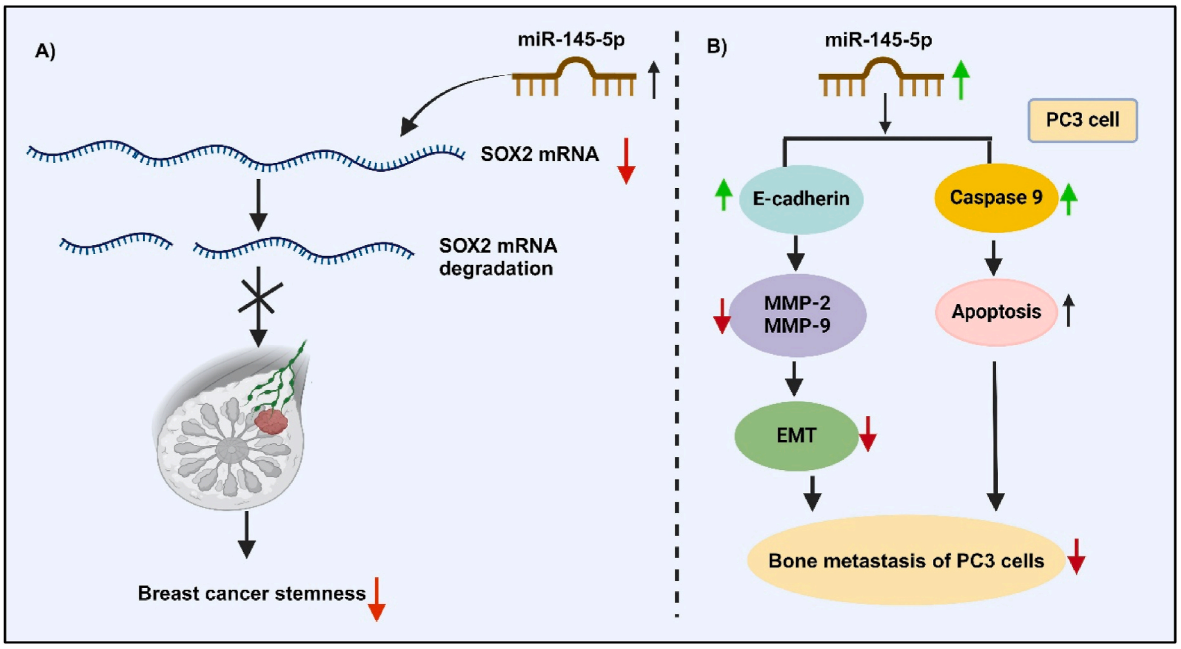

Fig. 6. Impacts of miR-145-5p in regulating breast and prostate cancer. A) miR-145-5p targets SOX2 mRNA, resulting in degradation that inhibits BC cell proliferation. B) E-cadherin is the epithelial marker upregulated by miR-145-5p and reduced expression of the MMP-2 and MMP-9, which results in EMT induction and apoptosis in PC3 cells. In addition, miR-145-5p-activated caspase-9 that mediates apoptosis of the bone metastasis of PC3 cells. These figures have been redrawn from Refs. [137,144].

through siRNA resulted in comparable declines in the invasion, migration, and viability of cervical cancer cells [140]. Another subsequent study revealed that miR-145 can potentially inhibit cervical cancer progression by targeting the WNT2B gene and disrupting the Wnt/β-catenin pathway. The experiments were conducted using HeLa and SiHa cell lines, along with 58 pairs of human CC tissue samples. The overexpression of WNT2B has been shown to reverse the inhibitory effects of miR-145 on cell proliferation and metastasis within cervical cancer (CC) cells [141].

Ovarian cancer is one of the most prevalent cancers in females, and miR-145-5p is considered a crucial regulator of epithelial ovarian cancer (EOC). Zhou and colleagues conducted a study to investigate the role of miR-145-5p in the etiology of EOC proliferation and metastasis by transfecting the SKOV-3 cell line with miR-145-5p mimics while also obtaining 18 EOC tissue samples and 18 samples from non-malignant-tissue-at-Xi'an-Gaoxin-Hospital. The results revealed that the expression of miR-145-5p was significantly reduced in EOC tissues, alongside an increase in SMAD4 levels. In addition, miR-145-5p acts as a tumor suppressor by playing a crucial role in preventing the development of malignancy and promoting the death of EOC cells through its targeting of SMAD4 [142]. Another subsequent study has shown that the overexpression of nerve growth factor (NGF) and tropomyosin receptor kinase A (TRKA) is associated with the upregulation of oncogenes like cMYC and VEGF, which are involved in the proliferation and angiogenesis of EOC. The overexpression of miR-145 reduced cell proliferation, migration, and invasion in EOC cells, which was associated with decreased levels of c-MYC and VEGF proteins. These findings indicate that the tumor-promoting effects of NGF/TRKA are influenced by the modulation of miR-145-5p levels in EOC cells, suggesting that upregulating miR-145-5p may serve as a potential therapeutic approach for EOC [143].

8. Diseases of the nervous system

MiR-145-5p dysregulation has been implicated in various nervous system disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD) [169,170]. Microglia are the principal immune cells in the brain that are activated in response to injury or diseases [171]. Microglial activation plays a significant role in the neuroinflammation associated with Parkinson's Disease (PD), highlighting its critical contribution to its etiology [172]. By modulating specific genes in microglia, miR-145-5p has the ability to reduce the excessive inflammatory response, potentially alleviating neurodegeneration in PD [173]. Nurr1 is indeed a member of the nuclear superfamily of orphan receptors, and it plays a critical role in modulating the dopamine phenotype 1. Its suppression has been associated with exacerbating the inflammatory response, subsequently contributing to PD neuronal cell death [174]. Xie et al. demonstrated that miR-145-5p is responsible for the suppression of Nurr1, and they further concluded that the use of an antagomir to miR-145-5p restored Nurr1 expression and improved neurological outcomes in MCAO/R rats, which serve as an *in vivo* model for PD [167]. Numerous studies have also tried to determine the causal link between miR-145-5p and AD. Some studies have demonstrated that AD patients exhibit reduced levels of miR-145-5p in the cerebrospinal fluid when compared to healthy controls [175]. It is well documented that Beta-amyloid, total tau, and phosphorylated tau 181 in the CSF are important biomarkers for the early diagnosis of AD [176].

miR-145 is abundantly expressed in vascular smooth muscle cells (VSMCs) and plays a vital role in their differentiation, implying that it may also have an effect on endothelial cells and influence overall vascular health. MiR-145 significantly promotes the contractile phenotype of VSMCs by inhibiting multiple factors that promote proliferation [177]. This regulatory mechanism facilitates a supportive environment for factors stabilizing the contractile phenotype [178]. Another research has shown that miR-145 is sufficient to trigger the differentiation of multipotent neural crest stem cells into VSMCs [179]. MiR-145 upregulation has been shown to induce the expression of various VSMC differentiation marker genes, thereby promoting the differentiation of VSMCs into a contractile phenotype [180]. Specifically, genes such as SM α-actin, calponin, and SM-MHC are upregulated due to the influence of miR-145 [180]. This differentiation is essential for maintaining vascular function and health, further highlighting the role of miR-145 in VSMC biology [181]. Recent studies have also shown that miR-145-5p can inhibit angiogenesis by regulating vascular endothelial growth

factor A (VEGF-A) and ANGPT2 in human brain microvascular endothelial cell injury models induced by oxygen and glucose deprivation [182]. Recently, Wenfeng and colleagues summarized that miR-145-5p may play a protective role in brain injury by suppressing the MMP-2-mediated Wnt/β-catenin pathway, which could enhance neural function, resolve blood-brain barrier disruption, alleviate brain edema, and reduce apoptosis [183].

9. Diseases of the endocrine system

MiR-145-5p is known to regulate the expression of genes crucial for insulin production and secretion in beta cells, thereby affecting glucose homeostasis. This microRNA's involvement in these processes highlights its significance in maintaining proper insulin function and overall glucose regulation [184]. Additionally, studies indicate that alterations in miR-145-5p levels can lead to impaired glucose-stimulated insulin secretion, further emphasizing its role in diabetes pathophysiology [185]. A recent study by Lucena and colleagues demonstrated that patients with low baseline plasma miR-145 levels had an increased risk of T2DM more frequently following the consumption of the low-fat diet [186]. ATP binding cassette A1 (ABCA1) is anticipated to be crucial for maintaining islet cholesterol homeostasis, supporting β-cell function, and influencing insulin resistance as well as T2DM [187]. In hepatic HepG2 cells, miR-145 regulates the expression levels of ABCA1 protein and influences cholesterol efflux, while in murine islets, increased miR-145 expression results in reduced ABCA1 protein levels, elevated total islet cholesterol and decreased glucose-stimulated insulin secretion. Conversely, inhibiting miR-145 resulted in increased ABCA1 protein expression and enhanced glucose-stimulated insulin secretion. Additionally, higher glucose concentrations in the culture media significantly reduced miR-145 levels in pancreatic beta cells [188].

Boufraqech and coworkers assessed the expression and function of miR-145 in thyroid cancer, exploring its potential clinical application as a biomarker. The findings revealed that miR-145 expression is significantly downregulated in thyroid cancer compared to normal tissues. When miR-145 was overexpressed in thyroid cancer cell lines, there was a decrease in cell proliferation, migration, invasion, VEGF secretion, and E-cadherin expression. Additionally, overexpression of miR-145 inhibited the PI3K/Akt pathway and directly targeted AKT3. In *vivo* studies using a xenograft mouse model increased miR-145 levels led to reduced tumor growth and metastasis and reduced VEGF secretion [189]. Numerous studies have explored the role of miR-145-5p in reproductive endocrinology, particularly with ovarian function, folliculogenesis, and steroid hormone production in the gonads [190]. Additionally, miR-145 has been associated with essential genes such as Activin A receptor type II (ACVRIB) and SMAD2, which are involved in the regulation of folliculogenesis [191]. During this process, the increase in oocyte size facilitates maturity, while the surrounding granulosa cells mediate proliferation and differentiation. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are also crucial in regulating folliculogenesis, alongside various intra- and extra-ovarian factors such as activins, inhibins, BMPs, and GDF-96 [192]. Research has increasingly demonstrated the involvement of activins in reproductive dysfunctions and cancers, highlighting their role in regulating folliculogenesis and the functions of follicles, notably in the maturation of oocytes and the modulation of granulosa cell proliferation [190,192]. Moreover, the ectopic expression of miR-145 has been shown to directly suppress both mRNA and protein levels of ACVRIB by targeting its 3′-UTR and disrupting activin-induced Smad2 phosphorylation, indicating its potential to inhibit granulosa cell proliferation [193].

10. Other cancers

Breast cancer (BC) is one of the most prevalent malignancies in women, with 2.3 million new cases reported worldwide in 2020, resulting in approximately 685,000 deaths, which accounts for 16 % of all cancer-related deaths [194]. MiR-145-5p functions as a cancer suppressor and regulates several genes involved in cancer development and metastasis [133,195]. It has been shown to directly or indirectly suppress metastatic signaling pathways, thereby downregulating the expression of different genes that play significant roles in the invasion and migration of cancer cells [133]. It is evidenced that miR-145-5p is significantly downregulated in breast cancer, as evidenced by numerous studies that indicate lower expression levels in breast cancer tissues compared to normal samples [196]. Additionally, a noteworthy correlation has been established between low levels of miR-145-5p and adverse clinical outcomes in breast cancer patients [144]. The sex-determining region Y box 2 (SOX2), a member of the SOXB1 family, is commonly upregulated in several types of cancer and has been identified as a target of miR-145-5p [144]. Through dual luciferase reporter assays, quantitative RT-PCR, and Western blot analyses validated that miR-145-5p mediates the suppression of SOX2, indicating that both miR-145-5p and SOX2 could serve as promising therapeutic targets for breast cancer treatment Fig. 6A) [164]. Other target genes associated with miR-145-5p in breast cancer include histone protein family member X (H2AFX) [164] and PD-L1, which is a crucial immune checkpoint molecule in breast cancer [197]. The downregulation of miR-145-5p is inversely correlated with PD-L1 overexpression, suggesting that restoring miR-145-5p expression in breast cancer may initiate apoptosis, leading to cell cycle arrest, and diminish cellular proliferation [197].

11. Therapeutic/targeting strategies for miR-145-5p

Therapeutic strategies targeting miR-145-5p hold promise for various clinical applications in different human diseases, including lung diseases and distinct cancer treatments [59,198,199]. Given its identified role as a tumor suppressor, one of the main approaches involves restoring its expression in cancer cells where it is downregulated. Therapeutic strategies involving miR-145-5p in lung diseases, particularly NSCLC, include improving the sensitivity of gefitinib-resistant cells via inhibition of NRAS and MEST expression [200]. Additionally, the LncRNA ROR/miR-145/FSCN1 axis can reverse epithelial-mesenchymal transition (EMT) in docetaxel-resistant lung adenocarcinoma cells, thereby sensitizing them to chemotherapy [201]. Targeting strategies for miR-145-5p include suppressing tumor cell proliferation by targeting OCT4, thereby impairing lung cancer development [202]. Furthermore, miR-145-5p can inhibit NSCLC cell migration and invasion by targeting PDK1 via the mTOR signaling pathway [55].

Another strategy focuses on the use of miR-145-5p mimics, which are synthetic molecules designed to mimic the natural function of the miRNA [198]. Once inside the cell, the mimic binds to 3′-UTR of the targeted mRNAs, leading to their degradation or translation repression [203]. In the context of COPD, miR-145-5p is often downregulated in lung tissues, which may contribute to airway remodeling and inflammation [77]. The employing of miR-145-5p mimics has shown potential in restoring its level, thereby reducing inflammation and improving lung functions [201]. Therapeutic strategies that involve intravesical administration of miR-145-5p mimics can target cancerous cells directly and potentially reverse malignant characteristics [201]. In some pathological conditions such as fibrosis or vascular smooth muscle cell dysfunction, the excessive expression of miR-145-5p can be blocked by antagomirs/miRNA inhibitors, preventing fibrosis progression or abnormal vascular remodeling in cardiovascular disease [204–206]. Additionally, nanoparticle-based delivery systems are being developed to improve the targeting and efficacy of miR-145-5p therapies. These systems can provide stable protection of the miRNA mimics from degradation and facilitate targeted delivery to tumor sites, thus maximizing therapeutic impact while minimizing off-target effects [207].

Gene therapy using viral vectors such as lentivirus or adeno-associated virus is another strategy to deliver miR-145-5p [208]. These vectors can be engineered to carry miR-145-5p expression, enabling sustained production of miR-145-5p inside the target cells

[208]. Therapeutic strategies targeting miR-145-5p in atherosclerosis include lentiviral vector-mediated delivery, which has been shown to enhance miR-145-5p expression and reduce plaque burdens in preclinical models [201,209]. In addition, CRISPR/Cas9-based miRNA editing is still in the early stages but offers a potential strategy to directly modulate the miR-145-5p level by editing genomic regions responsible for its expression [201,210,211]. Moreover, combining miR-145-5p mimics with existing chemotherapy regimens is being explored. This synergistic approach may enhance the sensitivity of cancer cells to chemotherapeutics by not only downregulating pro-survival signaling pathways but also by identifying cells to apoptotic stimuli [59].

12. Conclusion

MiR-145-5p plays a crucial role in regulating several important genes implicated in the progression of human diseases and is involved in various physiological processes, including cellular proliferation, differentiation, and apoptosis. While some diseases are worsened by increased expression of miR-145-5p, certain cancers are characterized by reduced levels of this microRNA. Therefore, miR-145-5p has a multifaceted role, with its expression capable of either worsening or improving outcomes across different diseases. A growing body of research has solidified the importance of miR-145-5p as a significant disease modifier, utilizing diverse models such as animal models, cell lines, and primary cells, which have offered valuable insights into its distinct roles. These investigations promise to enhance our understanding of miR-145-5p and the regulation of its target genes in various human diseases. Moreover, the dysregulation of miR-145-5p expression is associated with numerous respiratory, cardiovascular, and metabolic diseases, underscoring its potential as a therapeutic target or a biomarker candidate for disease diagnosis and prognosis.

CRediT authorship contribution statement

Md. Sohanur Rahman: Writing – review & editing, Writing – original draft, Conceptualization. **Suvankar Ghorai:** Writing – review & editing, Writing – original draft. **Kingshuk Panda:** Writing – original draft. **Maria J. Santiago:** Writing – original draft. **Saurabh Aggarwal:** Writing – review & editing. **Ting Wang:** Writing – review & editing. **Irfan Rahman:** Writing – review & editing. **Srinivasan Chinnapaiyan:** Writing – review & editing. **Hoshang J. Unwalla:** Writing – review & editing, Writing – original draft, Conceptualization.

Ethics statement

Not applicable.

Data statements

Not applicable.

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Abbreviations

ORF	Open reading frame
lncRNA	Non-coding RNA
siRNA	Circular RNA
BMI1	B Lymphoma Mo-MLV insertion region one homolog
circMET	Circular RNA
PVT1	Plasmacytoma variant translocation 1
JNK	Jun N-terminal kinase
MAP3K1	Mitogen-activated protein kinase 1
EMT	Epithelial-mesenchymal transition
ABCC1	ATP binding cassette subfamily C member 1
GOLM1	Golgi membrane protein 1
CAD	Coronary artery disease
PAD	Peripheral artery disease
HF	Heart failure
VSMC	Vascular smooth muscle cell
CGN	Chronic glomerulonephritis
NPC	Nasopharyngeal carcinoma
NSCL	Non-small cell lung cancer
HCC	Hepatocellular carcinoma
DKD	Diabetic kidney disease
BC	Breast cancer
PC	Prostate cancer
CC	Cervical cancer
PD	Parkinson's disease
AD	Alzheimer's disease
FSH	Follicle stimulating hormone
LH	Luteinizing hormone

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