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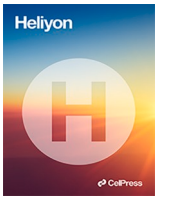

Review article

MicroRNAs and proteolytic cleavage of receptors in cancers: A comprehensive review of regulatory interactions and therapeutic implications

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A R T I C L E I N F O

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A B S T R A C T

Cancer remains a challenging disease worldwide, necessitating innovative approaches to better comprehend its underlying molecular mechanisms and devise effective therapeutic strategies. Over the past decade, microRNAs (miRNAs) have emerged as crucial players in cancer progression due to their regulatory roles in various cellular processes. Moreover, the involvement of unwanted soluble receptors has gained increasing attention because they contribute to tumorigenesis or drug resistance by disrupting normal signaling pathways and neutralizing ligands. This comprehensive review explores the intricate interplay between miRNAs and unwanted-soluble receptors in the context of cancer biology. This study provides an analysis of the regulatory interactions between miRNAs and these receptors, elucidating how miRNAs can either suppress or enhance their expression. MiRNAs can directly target receptor transcripts, thereby regulating soluble receptor levels. They also modulate the proteolytic cleavage of membrane-bound receptors into soluble forms by targeting sheddases, such as ADAMs and MMPs. Furthermore, the review delves into the therapeutic potential of manipulating miRNAs to modulate unwanted soluble receptors. Various strategies, including synthetic miRNA mimics or *anti*-miRNAs, hold promise for restoring or inhibiting miRNA function to counteract aberrant receptor activity. Moreover, exploring miRNA-based delivery systems may provide targeted and precise therapies that minimizing off-target effects. In conclusion, this review sheds light on the intricate regulatory networks involving miRNAs and unwanted soluble receptors in cancer biology thereby

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uncovering novel therapeutic targets, and paving the way for developing innovative anti-cancer therapies.

Abbreviations list

3′UTR Three prime untranslated region
ACE2 Angiotensin-converting enzyme 2
ADAMs A Disintegrin and Metalloproteinases
ADAMTs A Disintegrin and Metalloproteinase with Thrombospondin Motifs
CNTF Ciliary neurotrophic factor
CD23 Cluster of differentiation 23
CRC Colorectal cancer
CC Colon cancer
CRISPR-Cas9 Clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9
cMET Mesenchymal–epithelial transition tyrosine kinase
ESCC Esophageal squamous cell carcinoma
EGFR Epidermal growth factor receptor
ERK Extracellular signal-regulated kinase
GPI-anchored receptor Glycosylphosphatidylinositol-anchored receptor
GC Gastric cancer
GO Gene Ontology
HSCC Hypopharyngeal squamous cell carcinoma
HB-EGF Heparin-binding epidermal growth factor-like growth factor
HER2 Human epidermal growth factor receptor 2
HCC Hepatocellular carcinoma
IL-33 Interleukin-33
IgE Immunoglobulin E
LNA Locked nucleic acid
Let-7 Lethal-7
MICA Major histocompatibility complex (MHC) class I chain-related protein A
mRNA Messenger RNA
miRNA MicroRNA
MMPs Matrix Metalloproteinases
NOTCH1 Neurogenic locus notch homolog protein 1
NSCL Non-small cell lung cancer
NK cell Natural killer cell
OncomiR Oncogenic microRNA
pro-HB-EGF Pro-heparin binding epidermal growth factor-like growth factor
PC Pancreatic cancer
RNA Ribonucleic acid
RNAi RNA interference
RNA-seq RNA sequencing
RISC RNA-induced silencing complex
sPD-L1 Soluble programmed death-ligand 1
sFlt1 Soluble fms-like tyrosine kinase-1
sVEGFR1 Soluble vascular endothelial growth factor (VEGF) receptor-1
sACE2 Soluble angiotensin-converting enzyme 2
sST2 Soluble suppression of tumorigenicity 2
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
TNF Tumor necrosis factor
TNBCs Triple-negative breast cancer cells
TSCC Tongue squamous cell carcinoma
VEGFR Vascular endothelial growth factor receptor

1. Introduction

Cancer, the most pervasive health problem and the second-leading cause of mortality and morbidity globally, refers to a large, diverse group of diseases with an uncontrollable proliferation and growth of cells characterized by the ability to infiltrate and invade nearby normal tissues [1]. Despite improvements in disease screening and treatment, many challenges and concerns still exist. Conventional cancer therapies, including surgery, cytotoxic chemotherapy, and radiation therapy, as well as advanced and innovative cancer therapies (such as targeted therapy and immunotherapy, as single treatments or in combination), have shown varying degrees of success depending on the cancer type and stage [2,3]. Several factors contribute to the failure of these treatments, including tumor heterogeneity, metastasis, drug resistance, and drug delivery systems [4–6]. Therefore, understanding the underlying molecular and cellular characteristics of cancer and novel strategies is essential to overcome these challenges and develop therapeutic strategies.

Dysregulation of gene expression and disruption of signaling pathways and molecular networks, as well as epigenetic disorders, are the most important hallmarks of cancer and play an important role in maintaining oncogenic functions that lead to uncontrolled cell growth, proliferation, survival, and metastasis [7,8]. By understanding the specific signaling pathways that are aberrantly activated in different types of cancer, researchers can identify potential therapeutic targets. Targeting these pathways and other related factors with precision drugs can disrupt cancer cell growth and survival mechanisms, resulting in improved treatment outcomes [9]. In this context, soluble receptors are an important factor in cancer, and their role in tumor biology presents an opportunity for developing targeted therapies [10,11].

Dysregulated soluble receptors can interfere the intended ligand-receptor interactions, alter downstream signaling cascades, and contribute to disease progression [12,13]. Hence, a greater understanding of the regulatory mechanisms involved in the dysregulation of soluble receptors is essential for designing appropriate therapeutic strategies. One of the most important gene regulators is microRNAs (miRNAs). They are a class of small single-stranded non-coding RNA molecules that can play a significant role in the post-transcriptional regulation of gene expression. They can target and modulate the expression of soluble receptors or other molecules involved in their production or release [14–16].

The objective of this study was to explore the molecular mechanisms underlying the impact of miRNA on undesirable soluble receptors and their regulators in cancer, as they are potential therapeutic targets. Achieving this knowledge could aid in the creation of better treatment techniques, help with finding biomarkers, and present opportunities for using combination therapies to combat cancer.

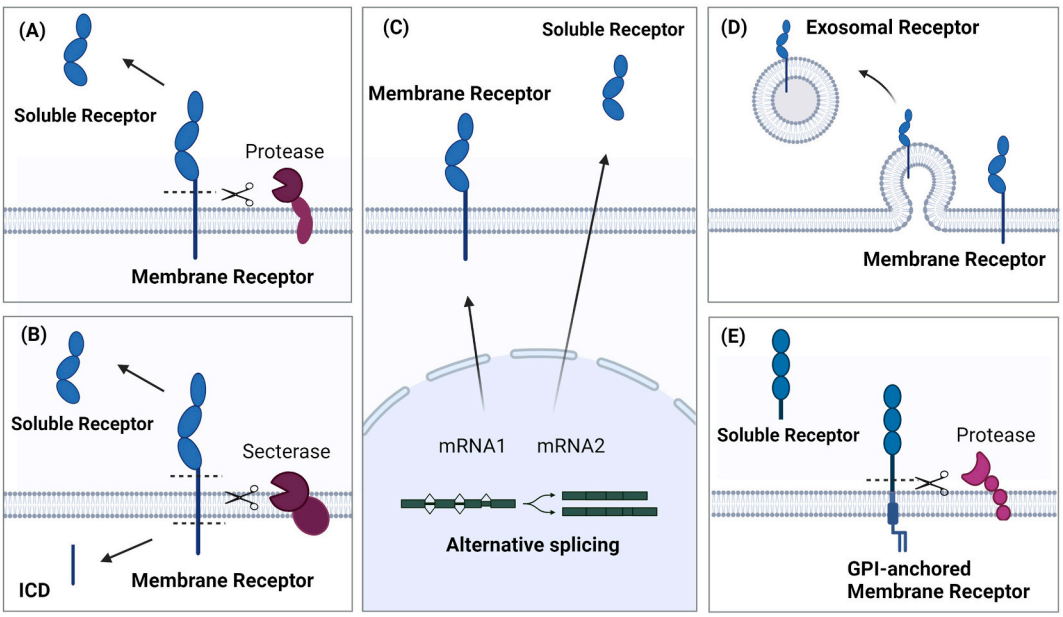

Fig. 1. Soluble receptor generation. (A) Proteolytic cleavage or shedding of a membrane receptor ectodomain by a surface protease, such as ADAMs. **(B)** Cleavage of a membrane receptor by γ-secretase and release of the receptor's intracellular domain (ICD). **(C)** Alternative splicing that leads to synthesis and release of soluble receptors lacking a transmembrane domain. **(D)** Release of membrane receptors in the context of extracellular vehicles, which is called exosomal receptor. **(E)** Cleavage of a GPI-anchored membrane receptor by a surface protease. **Abbreviations: mRNA** = Messenger Ribonucleic acid; **ICD** = Intracellular domain; **GPI** = Glycosylphosphatidylinositol.

Table 1
miRNA-dependent Regulation of ADAMs and MMPs in cancers.

miRNA	Disease/ conditions	Experimental models	Target	Expression in the disease/the result after the intervention	Refs
↑miR-720	TNBCs	*In vitro & in vivo*	↑ADAM8	miR-720 level was higher with high ADAM8 expression/miR-720 is a downstream target of an ADAM8-induced ERK signaling cascade, which promotes the invasive phenotype	[67]
↓miR-126	Prostate cancer	*In vitro*	↑ADAM9	Expression of miR-126 was decreased/miR-126 mimics suppressed prostate cancer cells progression through downregulation of ADAM9	[70]
↓miR-122–5p	Breast cancer	*In vitro*	↑ADAM10	miR-122–5p expression was lower/enforced increases of miR-122–5p inhibited ADAM10-mediated HER2 shedding thus overcoming trastuzumab resistance	[41]
↓miR-365	Breast cancer	*In vitro*	↑ADAM10	miR-365 was low-expressed/exogenous overexpression of miR-365 inhibited cell proliferation, migration and invasion by reducing the expression of ADAM10	[72]
↓miR-122	HCC	*In vitro*	↑ADAM10, ADAM17	miR-122 expression was decreased/restoration of miR-122 decreased the malignant phenotype by downregulation of ADAM10 and ADAM17	[73]
↓miR-122	HCC	*In vitro & in vivo*	↑ADAM17	miR-122 was downregulated/exogenous increases of miR-122 inhibited migration, angiogenesis, invasion, and tumorigenesis by downregulation of ADAM17	[74]
↓miR-3163	HCC	*In vitro & in vivo*	↑ADAM17	miR-3163 expression was decreased/overexpression of miR-3163 downregulated ADAM17, inhibited ADAM17-mediated cleavage and activation of Notch protein, enhancing the sensitivity to molecular targeted agents (*e.g.* sorafenib and decreased the EMT process)	[75]
↓miR-140–5p	HSCC	*In vitro & in vivo*	↑ADAM10	miR-140–5p was downregulated/restoration of miR-140–5p inhibited ADAM10-mediated Notch signaling pathway and suppressed invasion via repressing of ADAM10	[76]
↓miR-145	Glioblastoma	*In vitro*	↑ADAM17	miR-145 was downregulated/overexpression of this miRNA by mimics inhibited the expression of ADAM17 and enhanced temozolomide sensitivity	[77]
↓miR-122–5p	Osteosarcoma	*In vitro & in vivo*	↑ADAM10	miR-122–5p expression was decreased/miR-122–5p mimics inhibited ADAM10-mediated *E*-cadherin β-catenin signaling pathway and reduced cell proliferation, migration, and invasion of osteosarcoma cells by downregulation of ADAM10	[78]
↓miR-140–5p	TSCC	*In vitro*	↑ADAM10	miR-140–5p was downregulated and acts as a tumor suppressor/ overexpression of this miRNA repressed cell migration and invasion by downregulation of ADAM10	[79]
↓miR-203	HCC	*In vitro*	↑ADAM9	miR-203 expression was decreased/overexpression of miR-203 downregulated the expression of ADAM9 and inhibited cell proliferation, invasion and induced apoptosis	[80]
↓miR-126	HCC	*In vitro*	↑ADAM9	miR-126 was downregulated/miR-126 overexpression repressed the expression of ADAM9 and inhibited migration, invasion and metastasis	[81]
↓miR-1274a	HCC	*In vitro*	↑ADAM9	miR-1274a was upregulated after administration of sorafenib/ upregulation of miR-1274 suppressed the expression of ADAM9, mediating sorafenib target-chemotherapy by reducing the ADAM9-dependent MICA shedding and enhanced the antitumor immunity	[82]
↓miR-655–3p	HCC	*In vitro*	↑ADAM10	miR-655–3p was downregulated/overexpression of miR-655–3p reduced *E*-cadherin level and inhibited the ADAM10-mediated β-catenin pathway, resulting in reduced progression by repressing the expression of ADAM10	[84]
↓miR-451a	HCC	*In vitro*	↑ADAM10	miR-451a was downregulated in HCC/hucMSCs-derived exosomal miR-451a inhibited ADAM10 to suppress the paclitaxel resistance, proliferation, migration and invasion, promoted apoptosis and restricted the EMT	[85]
↑miR-145	HCC	*In vitro*	↓ADAM17, MMP9	miR-145 inhibited cell proliferation and growth activity via downregulation of ADAM17 and MMP9	[86]
↓miR-145	HCC	*In vitro*	↑ADAM17	miR-145 was downregulated/overexpression of miR-145 downregulated ADAM17 and inhibited cell invasion and intrahepatic metastasis	[87]
↓miR-126	ESCC	*In vitro & in vivo*	↑ADAM9	miR-126 was downregulated/ectopic expression of miR-126 downregulated ADAM9 and repressed cells proliferation and migration by inhibiting ADAM9-mediated EGFR–AKT signaling pathway	[126]
↓miR-126	GC	*In vitro*	↑ADAM9	miR-126 was downregulated/overexpression of miR-126 suppressed the expression of ADAM9 and reduced cell proliferation	[127]

(*continued on next page*)

Table 1 (*continued*)

miRNA	Disease/ conditions	Experimental models	Target	Expression in the disease/the result after the intervention	Refs
↓miR-129–5p	GC	*In vitro & in vivo*	↑ADAM9	miR-129–5p expression was downregulated/exogenous overexpression of miR-129–5p reduced cell proliferation and invasion ability by downregulation of ADAM9	[128]
↓miR-338–3p	GC	*In vitro*	↑ADAM17	miR-338–3p was downregulated/enforced expression of miR-338–3p inhibited proliferation, migration and invasion via downregulation of ADAM17	[129]
↓miR-320a	GC	*In vitro & in vivo*	↑ADAM10	The expression of miR-320a was reduced/ectopic miR-320a expression inhibited cell growth and enhanced the sensitivity to cisplatin via downregulation of ADAM10	[90]
↓miR-448	GC	*In vitro*	↑ADAM10	miR-448 expression was reduced/ectopic expression of miR-448 suppressed proliferation, colony formation, and invasion through negatively control of ADAM10	[130]
↓miR-126	PC	*In vitro*	↑ADAM9	miR-126 was downregulated/re-expression of miR-126 resulted in reduced cellular migration, invasion, and induction of epithelial marker *E*-cadherin via repression the expression of ADAM9	[131]
↑miR-328	PC	*In vitro*	↓ADAM8	Using the propofol upregulate the expression of miR-328/ upregulation of miR-328 suppressed the expression of ADAM8 and inhibited the proliferation and metastasis	[132]
↑miR-552	CRC	*In vitro & in vivo*	↓ADAM28	miR-552 was upregulated/enforced repression of miR-552 by antagomiR-552 contributed to upregulation of ADAM28 and suppressed cell proliferation and migration, and reduced capacity of tumorigenicity	[133]
↓miR-198	CRC	*In vitro*	↑ADAM28	miR-198 expression was reduced/overexpression of miR-198 inhibited cell proliferation and promoted apoptosis through blocking ADAM28-mediated JAK/STAT signaling pathway	[134]
↓miR-20 b	CC	*In vitro*	↑ADAM9	miR-20 b was expressed at lower levels in the 5-FU-resistant tissues and cells, the opposite was the case for expression of ADAM9 and EGFR/the overexpression of miR-20 b decreased the 5-FU resistance to induce apoptosis by suppressing ADAM9/EGFR	[135]
↓miR-126–3p	Melanoma	*In vitro*	↑ADAM9	miR-126–3p was downregulated in the dabrafenib-resistant sublines/miR-126–3p replacement inhibited cells proliferation and increased their sensitivity to dabrafenib via downregulation of ADAM9	[91]
↓miR-20 b	Bladder cancer	*In vitro*	↑MMP2	miR-20 b was downregulated/overexpression of miR-20 b resulted in a reduction in the proliferation and invasion of cancer cells by downregulation of MMP2	[136]
↓miR-126 and its complement miR-126*	Melanoma	*In vitro & in vivo*	↑ADAM9, MMP7	The expression levels of miR-126&126* were markedly declined/ replacement of these miRNAs reduced the proliferation, invasion and chemotaxis by downregulation of ADAM9 and MMP7	[89]
↓miR-140	Glioma	*In vitro*	↑ADAM9	miR-140 was downregulated/restoration of miR-140 inhibited proliferation, migration and invasion via suppressing ADAM9 expression	[137]
↓miR-590	NSCL	*In vitro & in vivo*	↑ADAM9	miR-140 was downregulated/delivery of miR-590 mimic and re-expression of that suppressed cell proliferation, migration, and invasion and tumorigenesis by repression of ADAM9	[138]
↓miR-152	NSCL	*In vitro*	↑ADAM17	miR-152 is downregulated/restoration of miR-152 reduced proliferation, migration and invasion by silencing of ADAM17 expression	[139]
↓miR-126–5p	NSCL	*In vitro*	↑ADAM9	miR-126–5p expression was downregulated and ADAM9 was upregulated/overexpression of miR-126–5p inhibited cells proliferation and promoted cell apoptosis via downregulation of ADAM9, and inhibition of the PTEN/PI3K/Akt signaling pathway and improving the sensitivity to cisplatin	[92]
↓miR-3174	Bladder cancer	*In vitro & in vivo*	↑ADAM15	miR-3174 expression was downregulated/overexpression of miR-3174 inhibited the proliferation due to the inhibition of ADAM15	[88]

Abbreviations list: ADAMs: A disintegrin and metalloproteinases; **MMPs**: Matrix Metalloproteinases; **MICA:** Major histocompatibility complex (MHC) class I chain-related protein A; **hucMSCs:** human umbilical cord mesenchymal stem cells; **EMT:** Epithelial-mesenchymal transition, **TNBCs:** Triple-negative breast cancer cells; **HCC:** Hepatocellular carcinoma cell; **HSCC:** Hypopharyngeal squamous cell carcinoma; **TSCC:** Tongue squamous cell carcinoma; **SMMC-7721:** Liver cancer cells; **ESCC:** Esophageal squamous cell carcinoma; **GC:** Gastric cancer; **PC:** Pancreatic cancer; **CRC:** Colorectal cancer; **CC:** Colon cancer; **NSCL:** Non-small cell lung cancer; **PTEN**: Phosphatase and tensin homolog; **PI3K:** Phosphoinositide 3-kinases; **AKT:** Protein kinase B.

** **↓ and ↑** Indicate downregulation and upregulation of the factor in disease condition, respectively.

2. Soluble receptors: functions and dysregulation

2.1. Soluble receptor generation

Soluble receptors are extracellular portions and ligand-binding sites of cell surface receptors that are released into the extracellular environment while maintaining high affinity for their ligands [13,17]. Soluble receptors can directly facilitate communication and cross-talk between different cells and organs and impact protein-protein interactions, thereby regulating various cellular processes [17]. Type 1 and 2 cytokine receptors, tumor necrosis factor (TNF) receptor family, chemokine receptors, immunoglobulin superfamily, and growth factor receptors are different examples of soluble receptors.

The production of soluble receptors can involve various mechanisms [Fig. 1 (A – E), & Table 1], and the relative proportions of these mechanisms can vary depending on the specific receptor and the context in which it is produced. Generally, the generation of soluble receptors can be modulated by two main mechanisms: (1) alternative splicing of receptor mRNA transcripts, leading to the production of multiple mRNA isoforms. Some of these isoforms may lack certain transmembrane domains or intracellular signaling domains, resulting in a soluble form of the receptor; (2) direct derivation from an existing full-length membrane-bound receptor, an irreversible post-translational modification called shedding, via proteolytic cleavage of the receptor ectodomain [18,19] [Fig. 1 (A)]. The shedding of receptors can be carried out by various proteases, also known as sheddase, which are involved in different cellular processes. Some surface proteases that have been implicated in the regulation of receptor shedding include A Disintegrin and Metalloproteinases (ADAMs), Matrix Metalloproteinases (MMPs), and A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTs) [20–23]. In addition, gamma-secretase and rhomboid proteases are other ways to release soluble receptors that act spontaneously [24,25] [Fig. 1 (B)].

Moreover, additional mechanisms of soluble receptor generation include the shedding of full-length receptors within the context of extracellular microvesicles, such as exosomes, as a compartment of the cell plasma membrane. Receptors released in this manner are not considered soluble forms because they retain their orientation and full-length structure as they are in the cell membrane. However, these released receptors can circulate and bind to ligands, thereby affecting their signaling properties [18,26,27]. In addition, they can modulate inter-organ crosstalk and integrate into the membranes of cells that previously did not have receptors [28]. Another less common mechanism of soluble receptor generation is ectodomain cleavage from glycosylphosphatidylinositol-anchored receptors (GPI-anchored receptors), which is applicable to the release of soluble ciliary neurotrophic factor (CNTF) receptors from skeletal muscle in response to peripheral nerve injury [29,30] [Fig. 1 (E)]. Noteworthy, the production of some soluble receptors typically involves several mechanisms, but these mechanisms may vary in their relative contributions and proportions.

2.2. Functions of soluble receptors

Soluble receptors play important physiological roles as signaling modulators. Their main function is to bind to ligands, such as growth factors or cytokines, and agonistically extend the signaling ability of their ligands. Furthermore, some soluble receptors can antagonistically act as ligand-neutralizing agents and decrease the availability and signaling of the ligands. They are also known as decoy receptors [13,17]. Under normal physiological conditions, soluble receptors help maintain a balance in cellular signaling, thereby ensuring proper cellular functions and homeostasis. They can fine-tune signaling responses, dampen excessive signaling, or prevent cell overstimulation [13,17]. However, the dysregulation of soluble receptors can occur in various disease states, including autoimmune diseases, viral infections, and cancer [11,13,19]. In these cases, unwanted soluble receptors can disrupt the normal signaling balance, leading to pathological consequences [31]. Specific soluble receptors have been implicated in various aspects of cancer development and progression. In this context, soluble immune checkpoints are one of the best examples that can be involved in the immune regulation, prognosis, and diagnosis of cancer [11,32]. Additionally, the soluble forms of receptor tyrosine kinases, such as epidermal growth factor receptor (EGFR), can sequester ligands and disrupt growth factor signaling, promoting tumor growth and resistance to therapies [33]. Another example is the soluble form of vascular endothelial growth factor receptor (sVEGFR), which can inhibit angiogenesis and the formation of new blood vessels crucial for tumor growth and metastasis [34]. In addition, functional disorders in factors involved in the production of soluble receptors, such as metalloproteinases, have also been reported in various cancers [35]. Thus, the production pathways of soluble receptors and the factors involved in their production and regulation may be

Table 2
miRNA-dependent regulation of ADAMs in resistance to treatments in cancers.

miRNA	Disease/conditions	Experimental models	Target	Sensitivity to Drug	Refs
↑miR-122–5p	Breast cancer	*In vitro*	↓ADAM10	↑Trastuzumab	[41]
↑miR-3163	HCC	*In vitro & in vivo*	↓ADAM17	↑Tosorafenib	[75]
↑miR-145	Glioblastoma	*In vitro*	↓ADAM17	↑Temozolomide	[77]
↑miR-451a	HCC	*In vitro*	↓ADAM10	↑Paclitaxel	[85]
↑miR-320a	GC	*In vitro & in vivo*	↓ADAM10	↑Cisplatin	[90]
↑miR-20 b	CC	*In vitro*	↓ADAM9	↑5-FU	[135]
↑miR-126–3p	Melanoma	*In vitro*	↓ADAM9	↑Dabrafenib	[91]
↑miR-126–5p	NSCL	*In vitro*	↓ADAM9	↑Cisplatin	[92]

Abbreviations list: ADAMs: A disintegrin and metalloproteinases; **HCC:** Hepatocellular carcinoma cell; **GC:** Gastric cancer; **CC:** Colon cancer.
** **↓ and ↑** Indicate downregulation and upregulation of the factor in disease condition, respectively.

important factors in carcinogenesis.

The translational potential of soluble receptors could be used as biomarkers or therapeutic targets. Since these receptors are soluble and circulate in the blood, they can be measured by convenient and non-invasive methods. In this context, the soluble form of receptor tyrosine kinase Axl, annexin A2, is reported to be a diagnostic biomarker of hepatocellular carcinoma, as well as soluble mesenchymal–epithelial transition tyrosine kinase (cMET) in ovarian cancer and soluble programmed death-ligand 1 (sPD-L1) in multiple myeloma [36–38]. Furthermore, evidence of the therapeutic potential of soluble receptors is in progress. In this context, the best-known example, etanercept, a recombinant soluble TNF receptor p75 Fc fusion protein, was designed to antagonize TNF in autoimmune diseases [39]. Another receptor-based therapeutic agent is aflibercept, a recombinant protein consisting of VEGF-binding portions of receptors, which is used for metastatic colorectal cancer (CRC) treatment [40]. Moreover, there is evidence regardingthe role of unwanted soluble receptors in drug resistance conditions (Table 2). Shedding of soluble human epidermal growth factor receptor 2 (HER2), which is mediated by proteolytic cleavage, decreases the ability of trastuzumab to bind to the membrane-bound HER2 receptors in breast cancer [41]. In parallel, tumor cells can evade immune detection by natural killer (NK) cells through the shedding of major histocompatibility complex (MHC) class I chain-related protein A (MICA), which hampers antitumor immunity. However, sorafenib can counteract this process by reducing ADAM9 levels, leading to decreased MICA shedding and improved responsiveness to NK cells in hepatocellular carcinoma (HCC) [42]. In general, these cases show that understanding the complex biology of soluble receptors and their ligands, along with knowing the factors regulating their release and production, is very

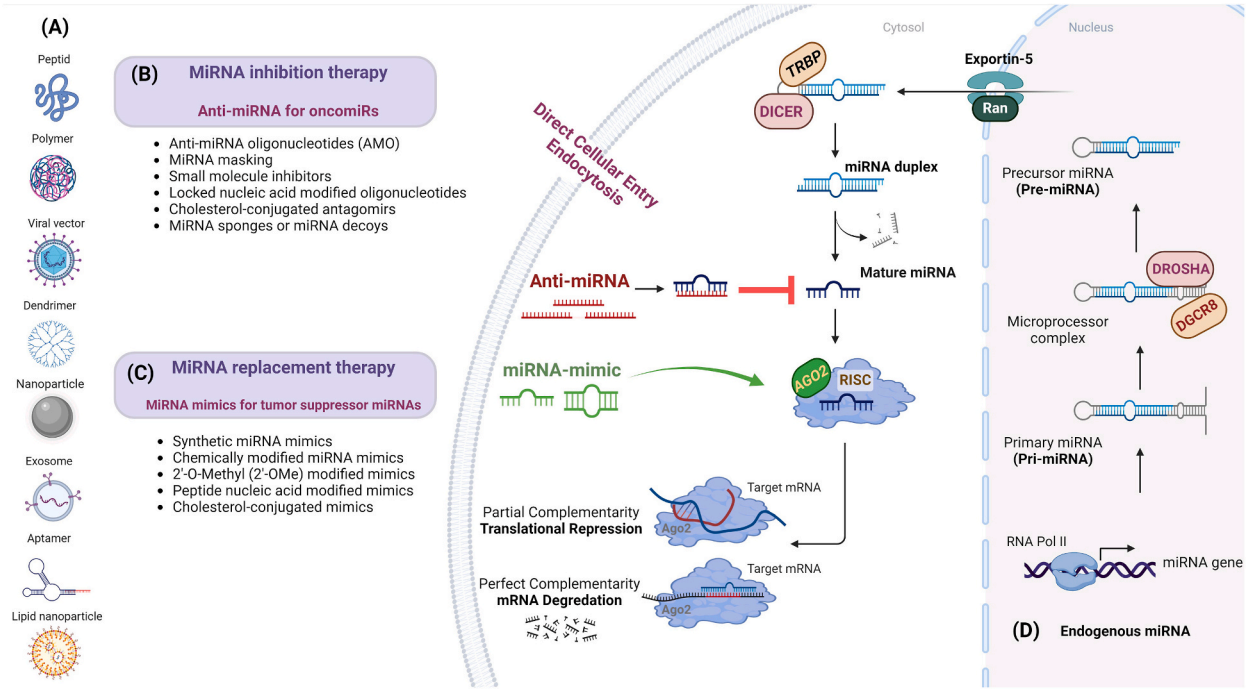

Fig. 2. miRNA-based therapeutic approaches and their mechanisms of action. A) miRNA delivery systems: they are employed for the targeted delivery of miRNA to specific cells and tissues. Various vehicles, including lipid nanoparticles, viral vectors, exosomes, and polymer-based carriers, are depicted facilitating miRNA transportation. These delivery systems protect miRNAs from degradation, enhance cellular uptake, and promote efficient release into the cytoplasm, thereby enabling precise modulation of gene expression for therapeutic applications. **B) miRNA inhibition therapy:** *Anti*-miRNAs are designed to inhibit endogenous miRNAs that contribute to disease progression by targeting disease-associated miRNAs. They are complementary to specific miRNAs and competitively bind to them. This prevents the native miRNAs from binding to their target mRNAs, thereby allowing the expression of target genes. They can be used to inhibit overactive oncogenic miRNAs or disease-promoting miRNAs, restoring the expression of their target genes and dampening disease progression. **C) MiRNA replacement therapy:** Synthetic miRNA mimics are designed to mimic the function of endogenous miRNAs that are downregulated or lost in a disease context, and they can be used to compensate for loss-of-function tumor suppressor miRNAs. The miRNA mimics are introduced into target cells to restore miRNA levels and bind to target mRNAs with sequence complementarity, leading to post-transcriptional gene silencing. **D) the stepwise process of miRNA biogenesis:** miRNA biogenesis begins in the nucleus with RNA polymerase II transcribing miRNA genes into primary miRNA transcripts (pri-miRNAs). The microprocessor complex, including Drosha and DGCR8, processes pri-miRNAs to create precursor miRNAs (pre-miRNAs) with hairpin structures. After nuclear export by Exportin-5, pre-miRNAs are cleaved by Dicer in the cytoplasm, forming a short duplex miRNA. This duplex unwinds, yielding a mature miRNA strand that integrates into the RNA-induced silencing complex (RISC) for gene regulation. The mature miRNA within the RISC complex binds to target messenger RNAs (mRNAs) through complementary base pairing. This interaction leads to translational repression or mRNA degradation, ultimately regulating gene expression. **Abbreviations**: **RNA pol III** = RNA polymerase III: **RISC** = RNA-induced silencing complex; **AGO2** = Argonaute-2 protein; **DROSHA** = Drosha ribonuclease III; **DGCR8** = DiGeorge critical region 8; **TRBP** = TAR RNA-binding protein; **DICER** = Dicer 1, ribonuclease III; **miRNA** = microRNA; **Ran** = RAs-related nuclear protein; **AntagomiR** = *Anti*-miRNA.

important for designing new therapeutic approaches. In many studies, the role of receptor-cutting enzymes in cell proliferation and growth, apoptosis, cancer, and tumor metastasis has been reported [43–47]. Moreover, the role of miRNAs in regulating the proteolytic pathway and these enzymes has been demonstrated [48].

3. MicroRNAs: key post-transcriptional regulators of gene expression

MicroRNAs (miRNAs) are a class of small single-stranded non-coding RNA molecules that play a crucial role in gene expression regulation. They function by binding to specific mRNA molecules through the recognition of the 3′-untranslated region (3′UTR), enhancing the degradation of mRNAs or translational repression [49]. Through transcript degradation and post-transcriptional control, miRNAs simultaneously control the expression of multiple genes, making them important regulators of various biological processes, including cell development, differentiation, proliferation, metabolism, immune response, and apoptosis [50]. The dysregulation of miRNAs has been implicated in many diseases, such as cancer [50–52]. They can act as oncogenic miRNAs, called oncogenic microRNAs (oncomiRs), which are usually upregulated or "tumor suppressor miRNAs", which are always downregulated in cancer [53,54]. These deregulations contribute to altered gene expression patterns and cellular processes, ultimately affecting tumor growth, metastasis, and response to treatment [55]. Understanding the specific miRNAs involved in different cancer types and their regulatory mechanisms is vital for the development of diagnostic tools, therapeutic interventions, and personalized treatment strategies for cancer [56] [Fig. 2 (A-D)]. Moreover, miRNAs structure, stability, and extracellular secretion to biofluids could make them a potent biofluid-based diagnostic biomarker in some types of cancers and diseases [57,58].

Because miRNAs have a tissue-specific expression profile and regulate several key pathways in tumorigenesis, cancer treatment using miRNAs is considered a strong alternative strategy to current treatments [56,59]. In addition, a comprehensive understanding of miRNA function and identification of the underlying pathways and their target genes will help better design therapeutic strategies.

4. Functional significance of miRNA-Soluble receptor interactions

4.1. MicroRNA-mediated modulation of soluble receptors

MiRNAs, as the key post-transcriptional regulator, can be implicated in the regulation of soluble receptors and their production pathways [60]. They can directly target the transcripts encoding these receptors, thereby regulating their expression levels. By binding to the 3′UTR or other regions of mRNA, miRNAs can prevent their translation or induce mRNA degradation, resulting in reduced soluble receptor production. This miRNA-mediated regulation can have profound effects on cellular signaling pathways that rely on soluble receptors [61]. A secreted form of VEGFR1, known as sVEGFR1, is produced through alternative splicing of the full-length *Vegfr1* gene [62]. sVEGFR1 acts as an inhibitory receptor by sequestering VEGF and antagonizing the activation of membrane-bound VEGFR1 [63]. According to research by Melton DW et al., inhibition of miR-125a-5p leads to increased sVEGFR1 production and decreased VEGF levels, indicating that miR-125a-5p directly targets *Vegfr1*, potentially contributing to the regulation of sVEGFR1 expression [61]. Additionally, Wu F et al. reported that miR-202–3p mediates the dysregulation of the interleukin-33 (IL-33) decoy receptor soluble suppression of tumorigenesis 2 (sST2), which is a crucial risk factor for hypertension. The study demonstrates that miR-202–3p significantly reduces the stability of soluble ST2-G mRNA and inhibits its natural expression. This effect is achieved through the binding of miR-202–3p to the 3′UTR region of soluble ST2 mRNA [64]. In another study, miR-421 was shown to be positively correlated with soluble angiotensin-converting enzyme 2 (sACE2) in the serum of diabetic patients; therefore, the decrease of this miRNA and the subsequent decrease of sACE2 are related to the severity of the SARS-CoV-2 in these patients [65]. Furthermore, miR-1246 modulates the expression of sACE2 in the small airway epithelium by targeting the 3′UTR of ACE2 mRNA [66].

4.2. Role of miRNA/ADAM protein axes in cancers

miRNAs have emerged as critical post-transcriptional regulators in the proteolytic cleavage of soluble receptors. They probably modulate this process by targeting the expression of key components involved in shedding events, including ADAMS and MMPs [60]. Therefore, miRNAs can influence the availability and activity of these enzymes, leading to the dysregulation of soluble receptor release into the extracellular space. Hence, various vital biological processes, such as cell signaling, survival, and apoptosis, can be disrupted by this regulatory mechanism [48]. Xu et al. showed that miR-28–3p downregulates the expression of ADAM17, which is a key component of ACE2 ectodomain shedding. This study showed that miR-28–3p mimic could play a potential therapeutic role in SARS-CoV-2 by targeting ADAM17 [48]. Another study reported that miR-720 is a downstream target of an ADAM8-induced ERK signaling cascade that promotes the invasive phenotype of triple-negative breast cancer cells (TNBCs), offering a poor prognosis [67]. In contrast, ADAM8 catalyzesectodomain shedding of cluster of differentiation 23 (CD23), alow-affinity IgE receptor that promotes inflammatory cytokine induction by macrophages [68]. Moreover, ADAM8 regulates immune function and cancer progression through the ectodomain shedding of proteins involved in cell adhesion and signaling pathways [69]. Therefore, based onthe changes in the expression of miRNAs and the role of ADAM8 in cancer, the relationship between this enzyme and miRNAs can be considered probable. In the context of cancer, Hua et al. revealed that miR-126 can act as a tumor suppressor in prostate cancer by targeting ADAM9, which plays a role in the metastasis and invasion of this cancer and contributes to the shorter survival of patients. Thus, the miR-126/ADAM9 axis could be considered a molecular target for advanced prostate cancer treatment [70]. On the other hand, ADAM9 facilitates the cleavage and release of growth factors (such as transmembrane pro-heparin-binding epidermal growth factor-like growth factor (pro-HB-EGF) precursors), suggesting that this protein may play an important role in tumor growth and cancer progression [71]. In

addition, another study identified ADAM10 as a direct target of miR-365 in breast cancer. Therefore,miR-365 could inhibit the proliferation and invasion of cancer cells through ADAM10 downregulation, thereby proposing the miR-365/ADAM10 axis as a new target for breast cancer treatment [72].

The liver-specific miRNA, miR-122, targets both ADAM10 and ADAM17 in HCC and has been proposed as a novel therapeutic agent in these patients [73,74]. Furthermore, ADAM17, which mediates the cleavage and activation of the neurogenic locus notch homolog (Notch) protein, was also identified as a target of miR-3163 in HCC. MiR-3163 inhibited the activation of the Notch signaling pathway, a key regulator of cellular survival, by binding to the 3′UTR region of ADAM17, thus mediating the transcription of pro-survival as well as anti-apoptosis genes and enhancing the sensitivity of HCC cells to molecular agents [75]. In this regard, another study related to the Notch1 signaling pathway showed that miR-140–5p, as a tumor suppressor, can inhibit the ADAM10-mediated Notch1 signaling pathway and thus suppress tumor migration and invasion in hypopharyngeal squamous cell carcinoma (HSCC) [76]. Another study reported that miR-145 enhances glioblastoma cell sensitivity to temozolomide by inhibiting ADAM17 [77]. In parallel, the interaction of several other miRNAs with ADAM regulation was shown to be associated with tumor progression, proliferation, metastasis, and drug sensitization in cancer [78–88]. These findings offer novel therapeutic approaches focusing on miRNAs and ADAMs. For example, a study revealed that ADAM9 and MMP7 are involved in the proteolytic cleavage of the heparin-binding EGF-like growth factor (HB-EGF), which is the predominant EGFR ligand. The findings of the study confirmed that miR-126 and miR-126* downregulate ADAM9 and MMP7, subsequently resulting in a decrease in HB-EGF activation and pro-neoplastic signals [89]. Furthermore, many studies have revealed that targeting ADAMs by miRNAs can also affect the drug sensitivity of tumor cells [41,75,77,90–92]. Table 1 summarizes the miRNA-dependent regulation of ADAMs and MMPs in different cancers.

5. Possible therapeutic implications

Indeed, the design of more efficient and specific treatments based on the biology of soluble receptors and the regulatory pathways of their release is an ongoing area of research in various fields. Understanding the impact of miRNA-mediated regulation on soluble receptor expression and function has significant therapeutic implications. As mentioned earlier, ADAMTs and MMPs play essential roles in the proteolytic cleavage of receptors. Developing selective inhibitors that specifically target these enzymes, such as miRNAs, could be a strategy to regulate the release of soluble receptors and modulate signaling pathways. MiRNAs could be designed to interfere with the proteolytic processing of receptors, ultimately affecting downstream signaling events. This approach may be beneficial in diseases in which excessive receptor cleavage contributes to pathogenesis. Manipulating the levels of specific miRNAs or using miRNA mimics/inhibitors, can either restore or disrupt the balance of soluble receptor expression. This can modulate signaling pathways, restore immune responses, or sensitize cancer cells to therapies. In this regard, several studies have demonstrated that miRNAs can influence drug sensitivity and counter drug resistance in cancer by regulating the expression of enzymes, including those involved in the release of soluble receptors [41,75,77,90–92]. For instance, the shedding of HER2 is mediated by ADAM10, resulting in a decrease in the function of trastuzumab to bind HER2 receptors. MiR-122–5p, as a tumor suppressor, could decrease HER2 shedding mediated by ADAM10, offering a novel strategy to use a combination of trastuzumab and miR-122 in breast cancer [41]. By modulating these enzymes, miRNAs offer a promising avenue to enhance the efficacy of treatments and overcome drug resistance in cancer therapy (Table 1).

Generally, miRNA therapeutic approaches are mainly divided into two strategies: (a) *anti*-miRNAs or antagomiRs, which suppress oncomiRs and restore their target genes, mainly tumor suppressors [Fig. 2 (B)]. They are often complementary single-stranded oligonucleotides that can bind to and sequester the endogenous miRNA, preventing mature miRNA from being processed by the RNA-induced silencing complex (RISC), leading to its exclusion from RISC and effectively inhibiting its regulatory function. By modulating endogenous miRNA activity, these inhibitors, or antagomiRs, offer a potential therapeutic approach for various diseases [59]. To this aim, several therapeutic strategies have been developed, such as *anti*-miRNA oligonucleotides [93], miRNA masking [94], small molecule inhibitors [95], locked nucleic acid (LNA)–modified oligonucleotides [96], cholesterol-conjugated antagomiRs [97], and miRNA sponges or miRNA decoys [98]. (b) miRNA-mimics, which restore the expression and loss-of-function of tumor-suppressor miRNAs and inhibit oncogenic genes [59]. In the administration of miRNA replacement therapy, the same sequence of reduced and natural miRNAs is used to reinstate the function of the downregulated tumor suppressor miRNA, which targets the same mRNAs and oncogenic pathways [99] [Fig. 2 (C)]. In this case, synthetic miR-34a, miR-16, and let-7 mimics provided a therapeutic benefit in reducing the tumor burden [100–102].

The delivery approaches of miRNA-based therapies can be classified into two main categories: direct local delivery to the targeted tissue or organ and systemic delivery [103]. Overall, these approaches are based on viral and non-viral miRNA delivery systems. Although non-viral vectors are considered safe, their drawback lies in their limited delivery efficiency. On the other hand, viral vectors exhibit higher transfection efficiency, but they encounter challenges related to immunogenicity and cytotoxicity [104]. In recent years, nanobiotechnology sciences have presented novel solutions to address the challenges associated with delivering drugs to their intended targets in cancer treatment while also producing safer and more effective treatment methods [105–107]. Generally, miRNA delivery systems that have been explored or developed for therapeutic applications include: lipid-based nanoparticles [108], degradable dendrimers and polymeric vectors [109], exosomes [110], aptamers [111], viral vectors [112], peptide-based delivery systems [113], and nanomaterials [114] [Fig. 2 (A)]. Fortunately, several miRNA-based clinical trials are conducted by biopharmaceutical companies, such as mIRNA Therapeutics, miRagen Therapeutics, Santaris Pharma, and Regulus Therapeutics [115]. In this regard, positively charged nanoparticles, particularly cationic liposomes, enhance the uptake of non-coding RNAs (ncRNAs) by target cells by interacting with the negatively charged cell membrane. This interaction addresses the hindrance posed by the negative charge and molecular weight of miRNAs, which can impede their passage through the cell membrane. Moreover, coating the nanocarrier with

tumor-specific targeting ligands boosts cellular uptake, reducing the risk of off-target effects of miRNA mimics or antagomirs on healthy cells [116]. For instance, MRX34, a liposomal encapsulated miR-34a mimic, is the first-in-human miRNA-based therapy performed by miRNA therapeutic in patients with refractory advanced solid tumors [117]. More recently, a preclinical study showed promising results of a lipid nanoparticle-based delivery system of miR-193 b mimic in patient-derived xenograft models of pediatric AML [118].

6. Future directions and challenges

The identification of clinically relevant miRNA-soluble receptor interactions often involves the use of high-throughput experimental approaches and computational tools. In this regard, miRNA profiling techniques, such as microarray and RNA sequencing (RNA-seq) that compare the expression of miRNAs in different tissues or biological samples lead to the recognition of differentially expressed miRNAs, that may play a role in the regulation of soluble receptors [119]. Furthermore, mass spectrometry-based proteomics can be used to identify and quantify the expression of soluble receptors and other relevant proteins in different cellular conditions or disease states [120]. Combining proteomic data with miRNA profiling can provide insights into potential miRNA-soluble receptor interactions. Other techniques, such as clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9 (CRISPR-Cas9)-based genetic screens or RNA interference (RNAi) libraries, can be used to systematically assess the impact of specific miRNAs on the expression or activity of their target soluble receptors [121]. These screens can help identify miRNAs that play an important role in regulating receptor expression. Target prediction algorithms, including TargetScan, miRanda, and DIANA-microT-CDS, and miRNA-mRNA interaction databases, such as miRTarBase, miRDB, and TarBase, provide a valuable resource for researchers studying miRNA-soluble receptor interactions [122]. After identifying potential miRNA targets, functional enrichment evaluation tools, such as Gene Ontology (GO) test or pathway enrichment analysis, can help realize biological processes and pathways affected by miRNA-mediated regulation of soluble receptors [123].

As miRNA-based therapy gains momentum for treating various human diseases, researchers are effectivelyexploring novel delivery strategies to optimize treatment outcomes with fewer side effects. These innovative approaches aim to improve the efficiency, specificity, and safety of miRNA delivery to target tissues and cells, thereby unlocking the full potential of miRNA-based therapeutics in clinical applications [124]. The successful translation of miRNA-based strategies from laboratory research to clinical applications heavily relies on the advancement and refinement of miRNA delivery vehicles [59,99]. These delivery vehicles are critical for ensuring efficient and targeted delivery of miRNAs to the intended sites in the body, ultimately enhancing the therapeutic efficacy and safety of miRNA-based treatments in real-world medical settings [103,125].

However, the review primarily focuses on theoretical possibilities rather than concrete clinical applications regarding the therapeutic potential of manipulating miRNAs to modulate soluble receptors. Incorporating more empirical evidence or clinical trials in future research is essential to support therapeutic implications. Additionally, despite providing insights, there is a need for further research to elucidate specific miRNA-target interactions and their functional consequences in cancer biology, allowing for the uncovering of novel regulatory mechanisms and therapeutic targets.

7. Conclusion

In conclusion, the intricate regulatory role of miRNAs in modulating the expression and function of soluble receptors holds significant therapeutic promise across diverse disease contexts, particularly in cancer, autoimmune, and inflammatory disorders. The dysregulation of miRNA-mediated interactions with soluble receptors can profoundly impact cellular signaling pathways, tumor microenvironment dynamics, and disease progression. Targeting key enzymes involved in receptor cleavage, such as ADAMTs and MMPs, presents a potential avenue for therapeutic intervention to regulate the release of soluble receptors and modulate downstream signaling cascades. By manipulating specific miRNA levels, it becomes feasible to restore the balance of soluble receptor expression, thereby altering downstream signaling events crucial for disease pathogenesis. Ongoing research aimed at elucidating the intricate miRNA-target interactions governing soluble receptor transcript regulation holds promise for uncovering novel mechanisms of gene regulation and therapeutic opportunities. Thus, the manipulation of miRNA expression or function emerges as a promising strategy to modulate soluble receptor levels and restore normal cellular signaling, offering potential avenues for the development of targeted therapeutic interventions in various disease contexts.

8. Search strategy

A systematic literature search was conducted to identify relevant studies focusing on the regulatory interactions between miRNAs and unwanted soluble receptors in cancer biology. The search strategy usedelectronic databases, including PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar. The search terms utilized various combinations of keywords related to miRNAs, soluble receptors, cancer, shedding, targeted therapy, and drug resistance. Additionally, reference lists of relevant articles and reviews were manually searched to identify additional studies. This study included original research articles, review articles, and meta-analyses published in English without restrictions on publication date. Experimental studies, clinical trials, and observational studies investigating the regulatory roles of miRNAs and soluble receptors in cancer progression, drug resistance, and therapeutic implications were considered. Exclusion criteria comprised studies not directly related to the topic, duplicate publications, conference abstracts, editorials, and commentaries. The selection process involved screening initial search results based on relevance, followed by a full-text assessment for eligibility. Data from selected studies were systematically extracted, including study design, investigated miRNAs and

soluble receptors, regulatory mechanisms, experimental or clinical outcomes, and implications for cancer biology and therapy. Synthesized data were thematically organized to provide a comprehensive overview of the regulatory interactions, key findings, mechanisms, and therapeutic implications, contributing to a deeper understanding of the complex regulatory networks involved in cancer progression and therapy.

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Declaration of competing interest

There is no conflict of interest.

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