Advances in miR-200c regulation of apoptosis, pyroptosis and autophagy in disease (Review)

XIAONA WANG[1*], HUA DU[2,3*] and YINGXU SHI[1]

[1]Department of Laboratory Medicine, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region 010010, P.R. China; [2]Department of Pathology, Basic Medical College, Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region 010010, P.R. China; [3]Department of Pathology, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region 010010, P.R. China

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Abstract. MicroRNAs (miRNAs or miRs) represent conserved non-coding RNAs responsible for the regulation of gene expression in a post-transcriptional manner. The dysregulation of miRNAs often leads to disease development and progress. In particular, miR-200c is one of the miR-200 family members, which is found deregulated in various pathologies and involved in the process of cancer progression through its participation in different molecular signaling pathways. Initially, miR-200c was regarded as an essential factor in metastases formation. Nevertheless, following the increase in knowledge about cell death signaling pathways, it became clear that miR-200c participates in various types of cell death such as apoptosis, autophagy and pyroptosis. The present narrative review primarily discusses the molecular mechanisms through which miR-200c regulates apoptosis, pyroptosis and autophagy and explores its potential therapeutic value.

Contents

Correspondence to: Dr Yingxu Shi, Department of Laboratory Medicine, Affiliated Hospital of Inner Mongolia Medical University, 5 Xinhua Street, Hohhot, Inner Mongolia Autonomous Region 010010, P.R. China
E-mail: shiyingxu@126.com

*Contributed equally

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1. Introduction

MicroRNAs (miRNAs or miRs) represent an evolutionarily conserved group of non-coding RNA sequences with sizes of 20-22 nucleotides. These small RNA molecules exert their effects on gene expression by interacting with the 3' untranslated region (3' UTR) of specific genes. Thus, miRNAs affect a broad spectrum of cellular events such as cell proliferation, differentiation, development and apoptosis (1-3). Accumulating research data indicate that aberrant levels of miRNAs can be causative factors in the pathogenesis of various conditions (4). For instance, in triple-negative breast cancer (TNBC), miR-429 tips the scales towards mischief by suppressing the tumor suppressor gene DLC1, resulting in enhanced proliferation, motility and invasiveness (5). Similarly, in lung cancer (LC), cell migration and invasiveness are reigned in through the action of miR-193b-3p on the PRNP gene (6). Clearly, these studies have brought to the fore the essential part that miRNAs play in the etiology of disease.

Prominent among such miRNAs is miR-200c, which belongs to the miR-200 family. Specifically, miR-200c exerts precise repression of the genes encoding for ZEB1 (7,8), ZEB2 (8,9) and FSTL1 (10). miR-200c plays an important role in controlling epithelial-mesenchymal transition (EMT) and, in consequence, in cancer metastasis. However, recent findings from cell death studies highlight yet another important aspect of miR-200c, this being the regulation of programmed cell death.

Cell death occurs along three major pathways that contribute to balanced tissue homeostasis and include apoptosis, pyroptosis and autophagy (11). These pathways do not exist as independent processes and interconnect forming complex interactions that are associated with disease initiation and progression (12-14). Despite the number of studies that have already demonstrated involvement of miR-200c in the regulation of apoptosis, pyroptosis and autophagy, research mostly focused on one particular death pathway and a single disease. This, in combination with highly varying expression of miR-200c among diseases and cells, indicates that the role of this miRNA in the control of programmed cell death in various diseases should be investigated.

The current review offers a comprehensive discussion on the function of miR-200c in the regulation of apoptosis,

autophagy and pyroptosis. The review stresses that it is important to clarify the molecular mechanism of miR-200c-induced apoptosis in different diseases. Additionally, the review evaluates the therapeutic potential of miR-200c from the perspectives of apoptosis regulation, nano-delivery strategies, and remodeling of the tumor microenvironment (TME). Collectively, this synthesis aims to provide a theoretical foundation for translating miR-200c-based therapeutic approaches into clinical practice.

2. Overview and physiological functions of miR-200c

Overview of miR-200c. miR-200c is a member of the miR-200 group, together with miR-141 residing in the same chromosomal locus of 12p13 (15,16). The transcript of the miR-200c gene is processed to form two miRNAs; namely miR-200c-3p and miR-200c-5p. Each of the aforementioned miRNAs is characterized by their unique seed sequence, where miR-200c-3p has the seed sequence 'AAUACUG' and miR-200c-5p the seed sequence 'GUCUUAC'. This property allows the identification of various mRNA targets for these miRNAs. Most of the studies have concentrated only on miR-200c-3p that targets key transcription factors associated with EMT like ZEB1 and ZEB2, as well as apoptosis-related genes such as BCL2 and XIAP. By contrast, miR-200c-5p has received relatively limited attention.

Apart from their unique target specificity, miR-200c abundance is regulated by complex epigenetic regulation involving DNA methylation and histone modifications. A study by Vrba *et al* (17) has shown that there exists an inverse relationship between miR-200c/141 CpG island methylation and the expression of miR-200c. This is because, in epithelial cells expressing miR-200c/141, the promoter region is marked with histone modifications such as H3K27ac and H3K4me3, which are histone marks associated with permissive environment; however, those that lack miR-200c/141 are often associated with non-permissive marks like H3K9me2 (17). Similarly, Wiklund *et al* (18) reported that transcription of the miR-200c/miR-141 cluster is suppressed by DNA methylation and H3K9me2 modifications.

Furthermore, demethylation is capable of promoting miR-200c gene expression. For instance, application of the demethylating drug, 5-aza-2'-deoxycytidine, significantly upregulates miR-200c gene expression (17). In another study, the use of CRISPR/dCas9-TET1 method was used by Zahraei *et al* (19) to design a specific gRNA, which targets the demethylase, TET1, to the miR-200c CpG island promoter region, leading to restoration of miR-200c gene expression. These findings underscore the complexity of miR-200c regulation and establish a foundation for developing therapeutic approaches that target epigenetic modifications associated with miR-200c expression.

Physiological functions of miR-200c. There exists a body of studies demonstrating that miR-200c lies at an important juncture during several physiological ceremonies, ranging from wound healing, to embryo development, and even mammary gland development (Fig. 1). Indeed, effective skin wound healing relies on a delicate act called re-epithelialization, which involves the cooperation of keratinocyte migration, proliferation and differentiation (20,21). Previous findings suggest that miR-200c acts as an inhibitor of re-epithelialization by suppressing keratinocyte migration and promoting cell differentiation, leading to a delay in wound closure (22). In other words, increased expression of miR-200c suppresses genes associated with migration, such as zinc finger E-box-binding homeobox 1 (ZEB1), serum response factor, chloride channel 4, RAS-related C3 botulinum toxin substrate 1 and hepatocyte growth factor receptor (Met), thus hindering keratinocyte migration. Concurrently, it upregulates differentiation-related genes, including keratin 1, loricrin and involucrin, resulting in an inhibition of wound healing (22).

E-cadherin is crucial for maintaining intercellular adhesion in epithelial tissues, and its expression is negatively regulated by ZEB1 and ZEB2. Upregulation of E-cadherin inhibits EMT. miR-200c-3p downregulates ZEB1 and ZEB2, thereby promoting E-cadherin expression and suppressing EMT. This regulation highlights the importance of miR-200c-3p in preserving epithelial phenotype integrity (8,23). Conversely, ZEB1 negatively regulates miR-200c, indicating a reciprocal negative feedback loop essential for epithelial stability (24). miR-200c is critical in multiple developmental processes. During heart development, miR-200c-3p inhibits the progression of EMT mediated by FSTL1, delaying the process of tissue regeneration in the heart (10). In tooth development, paired-like homeodomain transcription factor 2 which is the first molecular signal for tooth development, induces the expression of miR-200c/141. This inhibition of noggin which is an antagonist of bone morphogenetic protein (BMP) antagonist noggin, enhances BMP signaling, drives differentiation of dental epithelial stem cells, and facilitates enamel formation (25).

Regulation of miR-200c occurs in different embryological stages. For instance, regulation of miR-200c promotes embryonic stem cell differentiation toward endothelial progenitors and regulates embryonic angiogenesis via direct repression of ZEB1 gene (26). Vascular endothelial growth factor (VEGF) is an essential molecule for angiogenesis, whose expression may be induced by hydrogen sulfide (H_2S) (27,28). Importantly, according to Hu *et al* (29), H_2S downregulates the expression of miR-200c in human trophoblasts from the placenta and induces the synthesis of VEGF; thus, promoting the development of embryos' blood vessels. Conversely, when it comes to undifferentiated human embryonic stem cells (hESCs), miR-200c significantly suppresses GATA-binding protein 4 (GATA4), thereby inhibiting differentiation and embryoid body formation (30).

Additionally, miR-200c participates actively in embryonic development in early pregnancy and creates the pre-implantation environment (31). Zheng *et al* (32) showed that miR-200c downregulates fucosyl-transferase 4, suppressing Wnt/β-catenin signaling, and preventing successful embryo implantation. Pinopodes in the endometrium, which play a key role in receptivity necessary for embryo implantation, are also inhibited by miR-200c, reducing the chances of successful attachment (33).

In mammary gland development, miR-200c strongly inhibits the capability of mammary stem cells to form mammary ducts *in vivo* (34). All of these facts clearly highlight the important role played by miR-200c in the regulation of various processes in tissues.

3. Mechanisms of action of miR-200c in apoptosis,

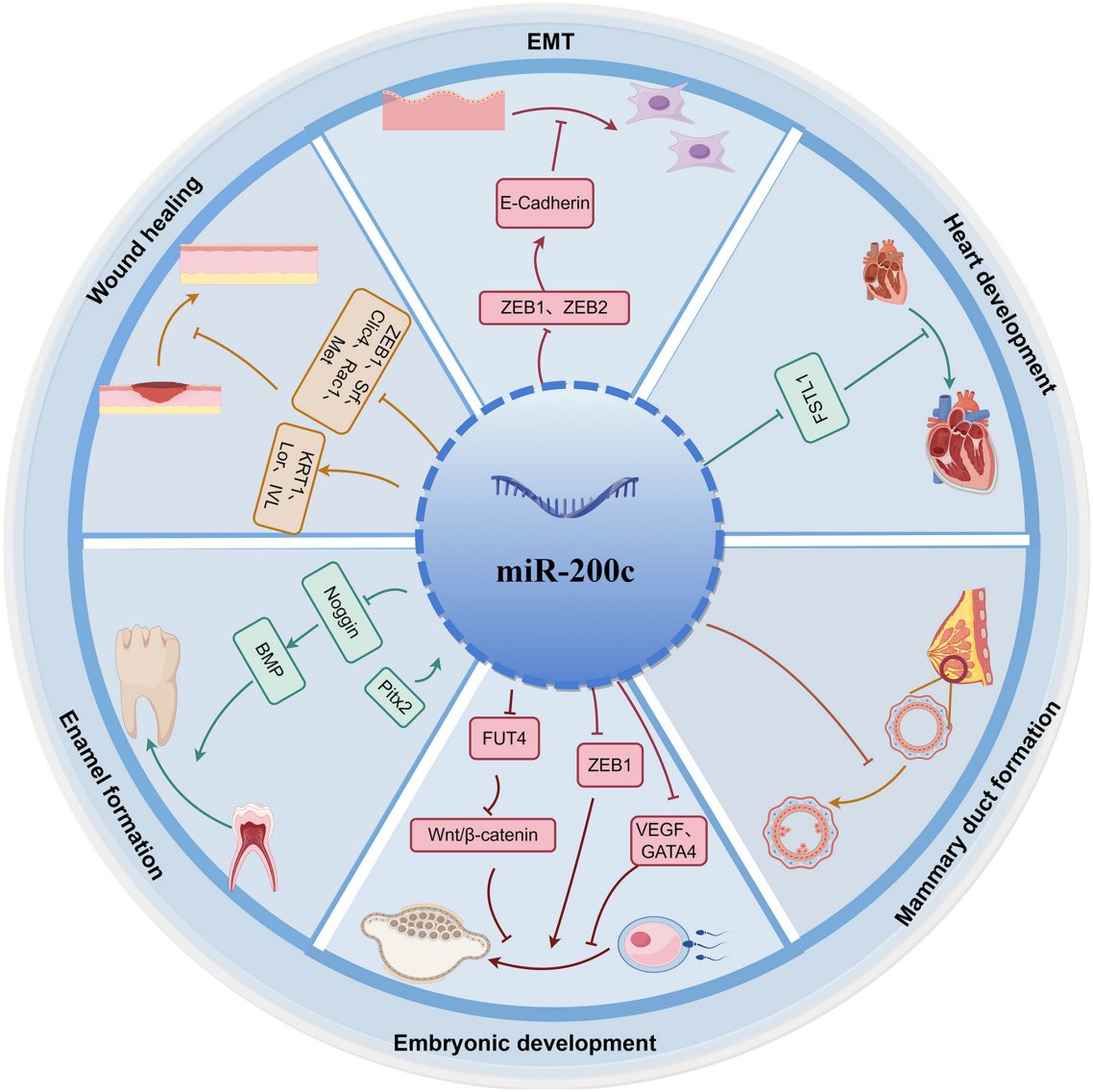

Figure 1. Overview of the physiological functions of miR-200c. Arrows indicate promotion (→) or inhibition (⊣) (figure generated with figdraw). miR, microRNA; EMT, epithelial-mesenchymal transition; ZEB, Zinc Finger E-box Binding Homeobox; VEGF, vascular endothelial growth factor; GATA4, GATA-binding protein 4; BMP, bone morphogenetic protein; Pitx2, paired-like homeodomain transcription factor 2; Clic4, chloride channel 4; Lor, loricrin IVL, involucrin; KRT1, keratin 1; FUT4, fucosyl-transferase 4; PDE7B, phosphodiesterase 7B; Srf, Serum response factor; Met, MET proto-oncogene, receptor tyrosine kinase; Rac1, Rac family small GTPase 1; FSTL1, Follistatin-like 1.

pyroptosis and autophagy

Apoptosis. It is clear that apoptosis plays a central role in programmed cell death which maintains cell number balance in order to preserve cellular and tissue homeostasis. Among all cell death mechanisms, apoptosis is considered essential due to its importance for the elimination of damaged, senescent and malfunctioning cells (35,36). An imbalance in the processes of cell life and death leads to the development of numerous pathological conditions (37,38). One of the principal regulators in this process is miR-200c, which performs a vital role in induction of apoptosis. Mechanisms of miR-200c-induced apoptosis include controlling intrinsic and extrinsic pathways of apoptosis induction, AKT-mediated apoptosis, and other target gene functions. Specific apoptosis-related molecular mechanisms regulated by miR-200c are represented in Fig. 2, while target genes are presented in Table I.

Regulation of intrinsic and extrinsic apoptotic pathways. Apoptosis is carried out via two pathways, namely the intrinsic pathway that arises from cellular dysfunction, and the extrinsic pathway that involves death signals from outside of the cell (39). Intrinsic pathway gets activated upon the disruption of cellular equilibrium caused by internal stress such as oxidative stress (OS) or damage to DNA, thus leading to programmed cell death. Mitochondrial outer membrane permeabilization (MOMP) is the critical event that characterizes this pathway (40,41). It is mediated by opposing actions of pro-apoptotic and anti-apoptotic members of BCL2 family (42). As a consequence of MOMP, Bax and Bak oligomerize to form pores on the surface of mitochondria, which results in the release of cytochrome c to the cytosolic compartment. Subsequently, released cytochrome c interacts with apoptotic protease-activating factor-1 (Apaf-1), allowing for the assembly of Apaf-1 into dATP-dependent complexes.

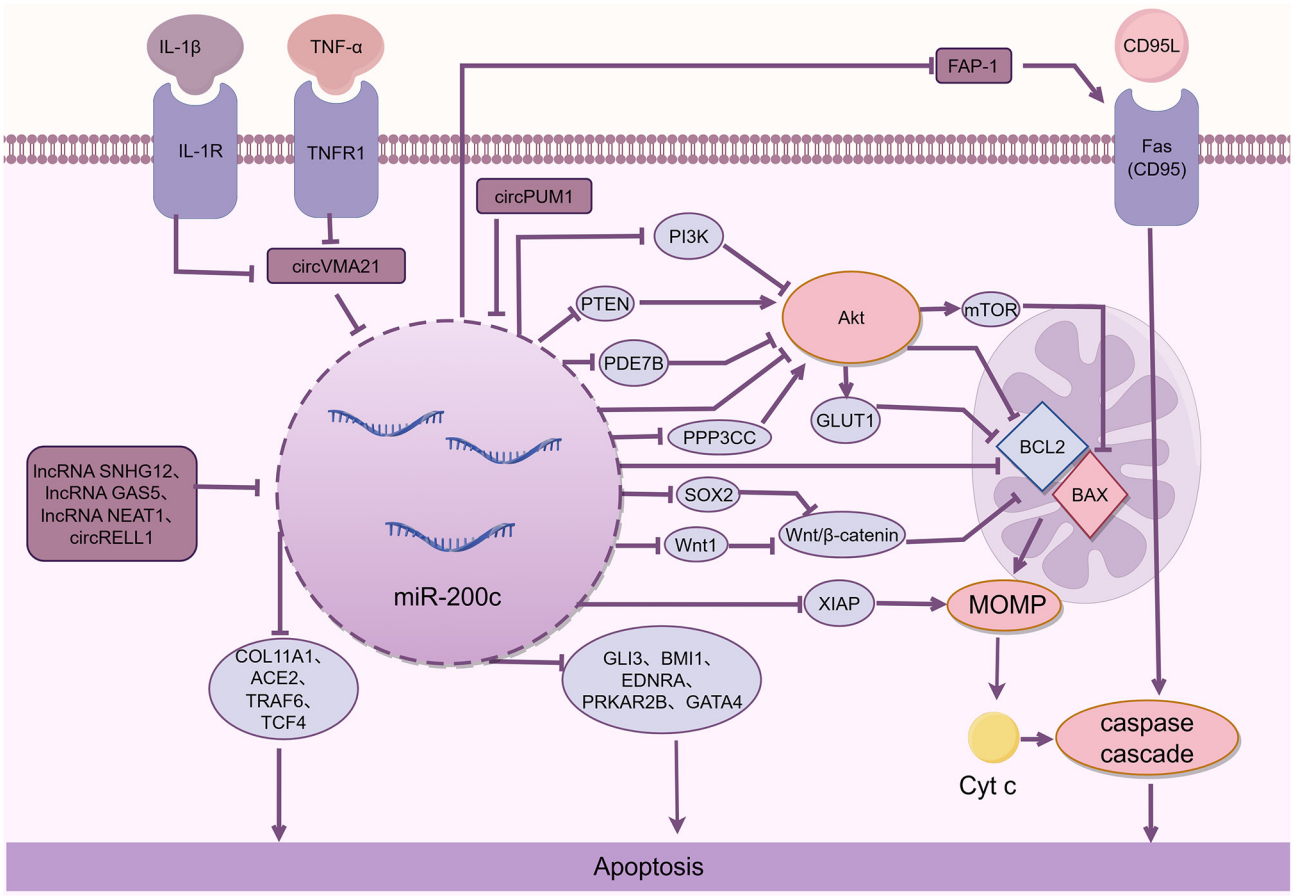

Figure 2. Molecular mechanisms through which miR-200c regulates apoptosis via multiple pathways. miR-200c is regulated by upstream factors, including inflammatory cytokines and non-coding RNAs, and directly targets a broad range of downstream genes to modulate apoptosis. Arrows indicate promotion (→) or inhibition (⊣) (figure generated with figdraw). miR, microRNA; lncRNA, long non-coding RNA; circ, circular RNA; MOMP, mitochondrial outer membrane permeabilization; COL11A1, collagen type XI alpha 1 chain; GATA4, GATA-binding protein 4; ACE2, angiotensin-converting enzyme 2; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; PTEN, phosphatase and tensin homolog deleted on chromosome 10; FAP-1, Fas-associated phosphatase-1; PPP3CC, protein phosphatase 3 catalytic subunit gamma; SOX2, SRY-box transcription factor 2; Wnt1, Wnt family member 1; PDE7B, phosphodiesterase 7B; GLI3, GLI family zinc finger 3; BMI1, BMI1 proto-oncogene, polycomb ring finger; EDNRA, endothelin receptor type A; PRKAR2B, protein kinase cAMP-dependent type II regulatory subunit beta; TRAF6, TNF receptor associated factor 6; TCF4, transcription factor 4; XIAP, X-linked inhibitor of apoptosis; BAX, BCL2-associated X protein; BCL2, BCL2 apoptosis regulator; GLUT1, Glucose transporter type 1.

These complexes are known as apoptosomes, which activate caspases and lead to apoptosis (43).

Conversely, the extrinsic apoptotic pathway is activated by extracellular death signals, such as Fas ligand (FasL/CD95L), via ligand-receptor interactions (44). Once this external signal binds to the corresponding receptor in the cell membrane, a death-inducing signaling complex that becomes active and sets a chain of reactions leading to apoptosis (45). While there may be variations in the beginning stage, both pathways will ultimately merge and end up activating the caspases, leading the cell towards programmed death (44,46). As indicated in the diagram below, miR-200c promotes apoptosis along both signaling pathways.

Intrinsic apoptotic pathway. The miR-200c facilitates intrinsic apoptosis by suppressing the amounts of several important anti-apoptotic proteins such as BCL2 and XIAP. As shown in patients with gastric cancer (GC) and LC, the microRNA induces apoptosis through the activation of a chain of programmed cell death by regulating both BCL2 and XIAP (47). This is also applicable to TNBC and intervertebral disc degeneration (IVDD) in that miR-200c initiates apoptosis by downregulating XIAP. In IVDD, circVMA21 serves as an upstream controller of the miR-200c-induced apoptosis. The inflammatory stimuli inflammatory cytokines interleukin-1β (IL-1β) and tumor necrosis factor-α reduce circVMA21 expression levels. Since circVMA21, as a miR-200c inhibitor, suppresses XIAP through binding to miR-200c, apoptosis occurs when the protein's amounts decrease due to the reduction of circVMA21, leading to a higher rate of death of nucleus pulposus cells (48,49). Collectively, these findings suggest that miR-200c-induced apoptosis via BCL2/XIAP suppression may represent a common regulatory mechanism rather than a disease-specific event, with variability arising from upstream modulators.

Additionally, the role of miR-200c in the regulation of intrinsic apoptosis is through modulating the Wnt/β-catenin pathway, which is intricately linked with mitochondria-driven apoptosis (50,51). Through suppression of the Wnt/β-catenin pathway, miR-200c promotes intrinsic apoptosis. This is evidenced by its ability to indirectly suppress Wnt/β-catenin pathway via SRY-box transcription factor 2 (SOX2) inhibition in renal cell carcinoma (RCC) cells, while in trophoblast cells

Table I. Target genes regulated by miR-200c and their mechanisms of action.

First author/s, year	Target gene	Disease	Strand specificity (3p/5p)	Verification method	Apoptosis direction	Regulatory mechanism	(Refs.)
Zhu *et al*, 2012	BCL2	GC and LC	-	Luciferase reporter assay and western blotting	Promotion	Direct targeted inhibition	(47)
Zhu *et al*, 2012; Ren *et al*, 2014	XIAP	GC, LC and TNBC	-	Luciferase reporter assay, RT-qPCR and western blotting	Promotion	Direct targeted inhibition	(47,48)
Cheng *et al*, 2018	XIAP	Intervertebral disc degeneration	-	Luciferase reporter assay and western blotting	Promotion	Regulated by circVMA21	(49)
Li *et al*, 2019	SOX2	RCC	-3p	Bioinformatics analysis, luciferase reporter assay, RT-qPCR and western blotting	Promotion	Inactivation of Wnt/β-catenin signaling pathway	(52)
Zhang *et al*, 2019	Wnt1	Preeclampsia	-	Luciferase reporter assay, RT-qPCR and western blotting	Promotion	Inactivation of Wnt/β-catenin signaling pathway	(53)
Schickel *et al*, 2010	FAP-1	Renal, ovarian and colorectal cancers	-	Luciferase reporter assay, RT-qPCR and western blotting	Promotion	Enhancement of Fas death receptor signaling	(55)
Zhang *et al*, 2019	PDE7B	TNBC	-	Luciferase reporter assay, RT-qPCR and western blotting	Promotion	Elevation of cAMP and inhibition of Akt activity	(68)
Shen *et al*, 2020	PTEN	Glaucoma	-	Bioinformatics analysis, luciferase reporter assay, western blotting and RT-qPCR	Inhibition	Activation of PI3K/AKT/mTOR pathway	(62)
Liao *et al*, 2013	PTEN	Pituitary adenoma	-3p	Bioinformatics analysis, luciferase reporter assay and western blotting	Inhibition	Activation of the PTEN/Akt signaling pathway	(61)
Anastasiadou *et al*, 2021	PPP3CC	Epithelial ovarian cancer	-3p	RT-qPCR and western blotting	Inhibition	Activation of the AKT signaling pathway	(70)
Yi *et al*, 2024	GLI3	LC	-	Luciferase reporter assay, RT-qPCR and western blotting	Promotion	Direct targeted inhibition	(71)
Cui *et al*, 2014	BMI1	Thymic lymphoma	-	Bioinformatics analysis, luciferase reporter assay, RT-qPCR and western blotting	Promotion	Direct targeted inhibition	(72)
Wei *et al*, 2018	EDNRA	GC	-	Luciferase reporter assay, RT-qPCR and western blotting	Promotion	Direct targeted inhibition	(73)
Xu *et al*, 2020	COL11A1	RCC	-5p	Luciferase reporter assay, RT-qPCR and western blotting	Inhibition	Regulated by lncRNA SNHG12	(80)
Xia *et al*, 2020	PRKAR2B	Prostate cancer	-3p	Bioinformatics analysis, luciferase reporter assay, RT-qPCR and western blotting	Inhibition	Direct targeted inhibition	(85)
Zhang *et al*, 2023	ACE2	Acute lung injury	-3p	Bioinformatics analysis, luciferase reporter assay, RT-qPCR and western blotting	Promotion	Inhibition of ACE2/ANG1-7 axis	(76)
Li *et al*, 2018	ACE2	Acute respiratory distress syndrome	-3p	Western blotting and RT-qPCR	Promotion	Regulated by lncRNA GAS5	(77)

Table I. Continued.

First author/s, year	Target gene	Disease	Strand specificity (3p/5p)	Verification method	Apoptosis direction	Regulatory mechanism	(Refs.)
Ding *et al*, 2024	TCF4	Osteoarthritis	-3P	Luciferase reporter assay, RT-qPCR, western blotting and RNA immunoprecipitation	Promotion	Regulated by circRELL1	(78)
Chen *et al*, 2017	GATA4	Ischemic heart disease	-	Luciferase reporter assay, RT-qPCR and western blotting	Promotion	Direct targeted inhibition	(79)
Zhang *et al*, 2022	TRAF6	Chronic periodontitis	-3P	Luciferase reporter assay, RT-qPCR and western blotting	Inhibition	Regulated by lncRNA NEAT1	(81)

GC, gastric cancer; LC, lung cancer; TNBC, triple-negative breast cancer; RCC, renal cell carcinoma; BCL2, BCL2 apoptosis regulator; XIAP, X-linked inhibitor of apoptosis; SOX2, SRY-box transcription factor 2; Wnt1, Wnt family member 1; FAP-1, Fas-associated phosphatase-1; PDE7B, phosphodiesterase 7B; PTEN, phosphatase and tensin homolog deleted on chromosome 10; PPP3CC, protein phosphatase 3 catalytic subunit gamma; GLI3, GLI family zinc finger 3; BMI1, BMI1 proto-oncogene, polycomb ring finger; EDNRA, endothelin receptor type A; COL11A1, Collagen type XI alpha 1 chain; PRKAR2B, protein kinase cAMP-dependent type II regulatory subunit beta; ACE2, Angiotensin converting enzyme 2; TCF4, transcription factor 4; GATA4, GATA binding protein 4; TRAF6, TNF receptor associated factor 6; RT-qPCR, reverse transcription-quantitative PCR; lncRNA, long non-coding RNA; circ, circular RNA.

isolated from rats with preeclampsia, miR-200c acts directly on Wnt1 (52,53).

Extrinsic apoptotic pathway. The induction of apoptosis mediated by extrinsic pathways is facilitated by miR-200c through the increased stimulation of Fas apoptosis pathway mediated by the repression of Fas-associated phosphatase-1 (FAP-1). CD95 (APO-1/Fas), which acts as the inducer for the apoptotic signaling, and is inhibited by FAP-1 through binding of the receptor (54). Schickel *et al* (55) demonstrated that miR-200c downregulates FAP-1 expression in clear cell RCC (CCRCC), RCC, ovarian cancer (OC) and colorectal cancer (CRC) cells, thereby enhancing Fas-mediated apoptosis (55). It has also been observed in endothelial cells in a similar fashion. Additionally, Jiang *et al* (56) observed that fluoride exposure induces apoptosis in endothelial cells through the induction of miR-200c-3p that represses FAP-1 resulting in Fas-mediated apoptosis. It should be noted that even though studies (55,56) have shown that miR-200c targets FAP-1 in cancer cells as well as in endothelial cells, the conservation of this function in other pathologies has not yet been determined.

AKT-mediated apoptosis. miR-200c influences the behavior of cells through regulation of apoptosis caused by AKT signaling, targeting several molecules, including phosphatase and tensin homolog (PTEN) and phosphodiesterase 7B (PDE7B). In other words, miR-200c exhibits dual impacts on apoptosis, depending on the type of disease. For instance, through PTEN and protein phosphatase 3 catalytic subunit gamma (PPP3CC) downregulation, miR-200c promotes AKT signaling activity and inhibition of apoptosis. At the same time, miR-200c can cause apoptosis either through inhibition of PDE7B or via inhibition of the PI3K-AKT pathway. The diverse roles of miR-200c-controlled pathways are discussed in detail below.

PTEN and the PI3K-AKT pathway. However, recent studies indicate that the inhibition of the PI3K-AKT pathway leads to increased cell death in various disorders (57). For example, miR-200c regulates the PI3K-AKT pathway within the trophoblasts in recurrent spontaneous abortion, resulting in a decrease in the BCL2/Bax ratio and cell apoptosis (58). The same can be said about pancreatic cancer where circPUM1 functions as a miR-200c-3p sponger; in the case of low expression levels of circPUM1, an increase in miR-200c-3p leads to the slowing of PI3K-AKT pathway activity and promotes apoptosis (59).

PTEN, an enzyme with dual activity of phosphatase towards lipids and proteins, acts against AKT through phosphorolyzing PIP3 into PIP2 (60). Considering PTEN's apoptosis-inducing function, downregulation of PTEN through miR-200c leads to AKT phosphorylation and subsequent induction of AKT pathway and inhibition of apoptosis. As observed by Liao *et al* (61), for instance, the expression of PTEN is decreased by miR-200c in pituitary tumors causing increased phosphorylated AKT levels with reduced cell apoptosis in pituitary adenoma (PA) cells. Similarly, miR-200c-3p induces PTEN suppression to increase phosphorylated AKT and mTOR levels, along with decreasing cleaved caspase-3 and Bax expression to inhibit apoptosis in glaucoma (62). Collectively, these findings suggest that miR-200c's regulation of apoptosis through the PTEN-AKT axis represents a critical anti-apoptotic mechanism across multiple disease contexts.

Other mechanisms regulating AKT activity. miR-200c regulates AKT signaling via processes other than those related to PTEN/PI3K modulation. In their study, Zhao *et al* (63) observed that miR-200c suppresses phosphorylated AKT levels and subsequent GLUT1 expression in Wilms tumor, thus promoting apoptosis. Besides, miR-200c regulates AKT signaling by affecting intracellular cAMP concentrations. Increased intracellular cAMP levels reduce AKT signaling (64,65), while PDEs, enzymes responsible for regulating intracellular cAMP degradation, are among the targets of miR-200c (66,67). Zhang *et al* (68) revealed that miR-200c suppresses PDE7B, which led to the increase in intracellular cAMP, inhibition of AKT signaling, and promotion of apoptosis in TNBC cells.

The next dimension of miR-200c is revealed by its involvement in inhibiting apoptosis through other targets that regulate AKT. For instance, the calcineurin-gamma subunit is involved in mediating the calcium/calmodulin-dependent serine/threonine phosphatase and is regarded as a tumor suppressor in apoptosis. The target gene of miR-200c-3p includes PPP3CC (69). In epithelial OC, miR-200c-3p-mediated PPP3CC inhibition leads to AKT activation, increased BCL2 expression and decreased caspase-3, collectively inhibiting apoptosis (70).

Regulation of apoptosis via other target genes. Outside the AKT pathway, miR-200c acts to induce apoptosis via targeting an array of genes, including those related to development (GLI3 and GATA4), inflammation (TRAF6) and cell-cycle regulation (BMI1). The aforementioned list indicates the complexity and interweaving aspects that contribute to the effects of miR-200c in apoptosis. For instance, miR-200c drives apoptosis in LC, thymic lymphoma, and GC by inhibiting GLI3, BMI1 and EDNRA, respectively (71-73). Also, it should be noted that angiotensin-converting enzyme 2 (ACE2), one of the confirmed miR-200c-3p targets, serves in various protective functions in lungs (74,75). Both damage to the lungs due to seawater aspiration causing acute lung injury (ALI) and the more extensive condition of acute respiratory distress syndrome (ARDS) are governed by miR-200c-3p, which facilitates apoptosis by reducing ACE2 levels. More precisely, in the case of ALI, the increased apoptosis results from inhibition of the ACE2/ANG1-7 feedback mechanism (76). In ARDS, inhibition of the long non-coding RNA (lncRNA) GAS5 molecule causes miR-200c-3p upregulation, reduced ACE2, and apoptosis in A549 cells (77). Similarly, Ding *et al* (78) reported that circRELL1 knockout elevates miR-200c-3p in osteoarthritis (OA), inhibiting TCF4 expression and leading to increased apoptosis. In ischemic heart disease, miR-200c induces cardiomyocyte apoptosis by directly suppressing GATA4, highlighting potential therapeutic implications (79).

Conversely, miR-200c exhibits anti-apoptotic effects in RCC, prostate cancer (PCa), and chronic periodontitis (CP). The possible mechanism behind these anti-apoptotic functions involves factors specific to the different cells and competition against upstream non-coding RNAs. However, the actual pathway needs further investigation. For example, in RCC, the lncRNA SNHG12 has been shown to be involved in sequestering miR-200c-5p; upon downregulation of SNHG12, there is upregulation of miR-200c-5p, which results in decreased levels of collagen type XI alpha 1 chain mRNA and apoptosis (80). Similarly, depletion of NEAT1 in CP leads to an increase in miR-200c-3p, causing downregulation of TRAF6 and thus preventing apoptosis (81). Interestingly, TRAF6 is generally recognized as a key mediator of pro-inflammatory responses in canonical immune signaling pathways, and its downregulation can suppress inflammation and promote cell survival (82,83). Therefore, the observed downregulation of TRAF6 by miR-200c-3p in CP suggests that miR-200c-3p may exert anti-apoptotic effects within this inflammatory microenvironment. Similar anti-apoptotic effects of miR-200c-3p have also been reported in PCa. Lin *et al* (84) reported that miR-200c-3p directly exerts anti-apoptotic effects in PCa cells (84). Additionally, in PCa, miR-200c-3p directly exhibits anti-apoptotic properties, with Xia *et al* (85) reporting inhibition of apoptosis via specific targeting of PRKAR2B.

In summary, miR-200c regulates apoptosis via multiple mechanisms, exhibiting both pro- and anti-apoptotic effects depending on the cellular context (Fig. 3). Current evidence indicates that miR-200c predominantly promotes apoptosis in diseases such as GC, TNBC and Wilms tumor, whereas it inhibits apoptosis in pituitary tumors, glaucoma, epithelial OC, PCa and CP. Several factors explain these context-dependent effects, including: i) Cell- and tissue-specific gene expression and signaling differences; ii) EMT status, with mesenchymal cells typically less sensitive to apoptosis (86-88); iii) distinct seed sequences of miR-200c-3p and miR-200c-5p, targeting different mRNAs; iv) differential targeting of pro- or anti-apoptotic nodes within signaling pathways; and v) composition of competing endogenous RNA regulatory networks, where circular RNAs and lncRNAs competitively bind miR-200c, altering target gene expression and influencing apoptosis outcomes.

Pyroptosis. Pyroptosis is an inflammatory form of programmed cell death crucially involved in the onset and progression of various diseases. The activation of the NLRP3 inflammasome and the cleavage of gasdermin D (GSDMD) constitute the core mechanisms underlying pyroptosis (89). Pyroptosis is initiated via two distinct pathways: The classical and non-classical pathways. The classical pathway involves assembly of the NLRP3 inflammasome, consisting of NLRP3, apoptosis-associated speck-like protein, and caspase-1, as well as caspases -4, -5, and -11. Activated caspase-1 subsequently cleaves GSDMD, into N-terminal and C-terminal fragments (90). By contrast, the non-classical pathway involves direct activation of human caspase-4/5 or mouse caspase-11 by lipopolysaccharides derived from Gram-negative bacteria. These caspases similarly cleave GSDMD (90,91). The N-terminal fragment of GSDMD forms pores in the cell membrane, leading to cell swelling and rupture, and converts inactive pro-inflammatory cytokines pro-IL-1β and pro-IL-18 into their mature forms. This process amplifies local inflammatory response, ultimately driving pyroptotic cell death (92,93).

Existing research confirms miR-200c is extensively regulates pyroptosis. However, current evidence pertains exclusively to the classical NLRP3/caspase-1 pathway; no studies to date have examined miR-200c involvement in the non-classical caspase-4/5/11 pathway. Future research is necessary to address this knowledge gap.

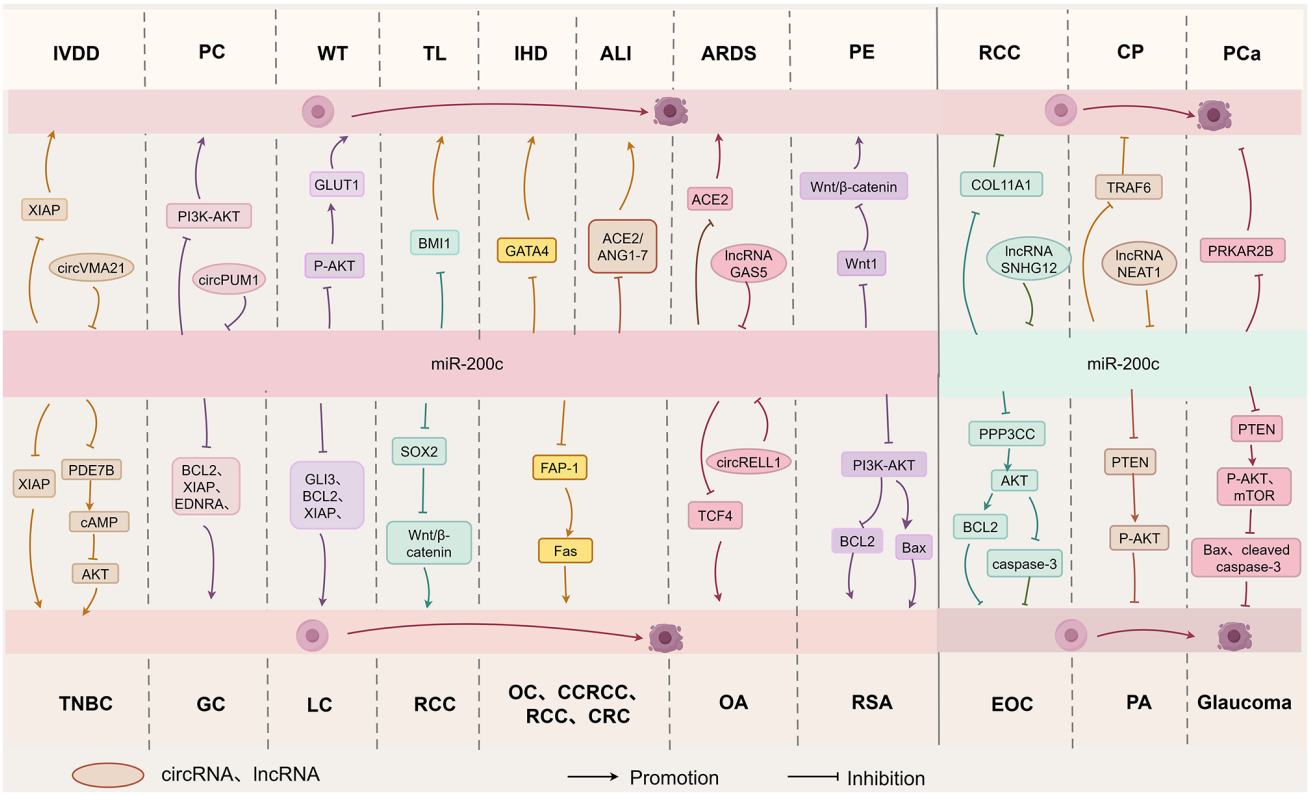

Figure 3. Molecular mechanisms of miR-200c-mediated apoptosis in various diseases. Arrows indicate promotion (→) or inhibition (⊣) (figure generated with figdraw). IVDD, intervertebral disc degeneration; PC, pancreatic cancer; WT, Wilms tumor; TL, thymic lymphoma; IHD ischemic heart disease; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; PE, preeclampsia; TNBC, triple-negative breast cancer; GC, gastric cancer; LC, lung cancer; RCC; renal cell carcinoma; OC, ovarian cancer; CRC, colorectal cancer; CCRCC, clear cell RCC; OA, osteoarthritis; RSA, recurrent spontaneous abortion; CP, chronic periodontitis; PCa, prostate cancer; EOC, epithelial OC; PA, pituitary adenoma; lncRNA, long non-coding RNA; circRNA, circular RNA; GATA4, GATA-binding protein 4; ACE2, angiotensin-converting enzyme 2; FAP-1, Fas-associated phosphatase-1; PPP3CC, protein phosphatase 3 catalytic subunit gamma; PTEN, phosphatase and tensin homolog deleted on chromosome 10; COL11A1, collagen type XI alpha 1 chain; TRAF6, TNF receptor associated factor 6; PDE7B, phosphodiesterase 7B; SOX2, SRY-box transcription factor 2; BCL2, BCL2 apoptosis regulator; XIAP, X-linked inhibitor of apoptosis; GLUT1, glucose transporter type 1; GLI3, GLI family zinc finger 3; BMI1, BMI1 proto-oncogene, polycomb ring finger; Fas, Fas cell surface death receptor; EDNRA, endothelin receptor type A; ANG1-7, Angiotensin 1-7; TCF4, transcription factor 4; Wnt1, Wnt family member 1; BAX, BCL2-associated X protein; PRKAR2B, protein kinase cAMP-dependent type II regulatory subunit beta; XIAP, X-linked inhibitor of apoptosis; GLUT1, Glucose transporter type 1; GLI3, GLI family zinc finger 3; TCF4, transcription factor 4.

In diabetes-related complications, such as diabetic retinopathy (DR) and diabetic nephropathy (DN), miR-200c mediates pyroptosis predominantly through activation of the NLRP3 inflammasome, though pathways differ diseases. Li *et al* (94) demonstrated that miR-200c-3p promotes pyroptosis in human retinal microvascular endothelial cells during DR by downregulating SLC30A7, thus activating the NLRP3 inflammasome. In DN, hyperglycemic conditions concurrently induce lncRNA MALAT1 and miR-200c, synergistically inhibiting NRF2 and elevating miR-200c-3p expression in exosomes derived from glomerular mesangial cells. Both mechanisms can activate the NLRP3 inflammasome, exacerbating podocyte pyroptosis. By contrast, the lipid-lowering agent atorvastatin and the traditional Chinese medicinal formula Tongluo Yishen confer renal protection by blocking these pathways (95,96).

Notably, in inflammatory bowel disease (IBD), miR-200c suppresses pyroptosis. Specifically, miR-200c-5p directly targets and inhibits NEK7, a critical activator of the NLRP3 inflammasome, thus reducing pyroptosis in intestinal epithelial cells (MODE-K) cells. This inhibition attenuates intestinal inflammation and mitigates disease progression in IBD (97).

In summary, miR-200c exhibits disease-specific regulatory roles in pyroptosis, promoting it in diabetic complications while inhibiting it in inflammatory bowel disease. This specificity provides a theoretical foundation for developing miR-200c-targeted therapeutic strategies against pyroptosis-associated diseases.

Autophagy. Autophagy is a highly conserved process of cellular self-degradation process in which substantial amounts of cytoplasmic content and organelles are encapsulated within double- or multi-membraned autophagosomes and subsequently delivered to lysosomes for degradation (98,99). Under pathological conditions, radiation-induced autophagy typically exerts a cytoprotective effect, thereby reducing the sensitivity of tumor cell sensitivity (100). For example, Sun *et al* (101) demonstrated that miR-200c inhibits protective autophagy induced by radiation in BC cells by downregulating UBQLN1, leading to decreased LC-II and increased p62 expression, thus enhancing radiosensitivity. In a cerebral ischemia model, the lncRNA MALAT1 competitively binds to miR-200c-3p. Knockdown of MALAT1 increases miR-200c-3p levels, resulting in downregulated SIRT1,

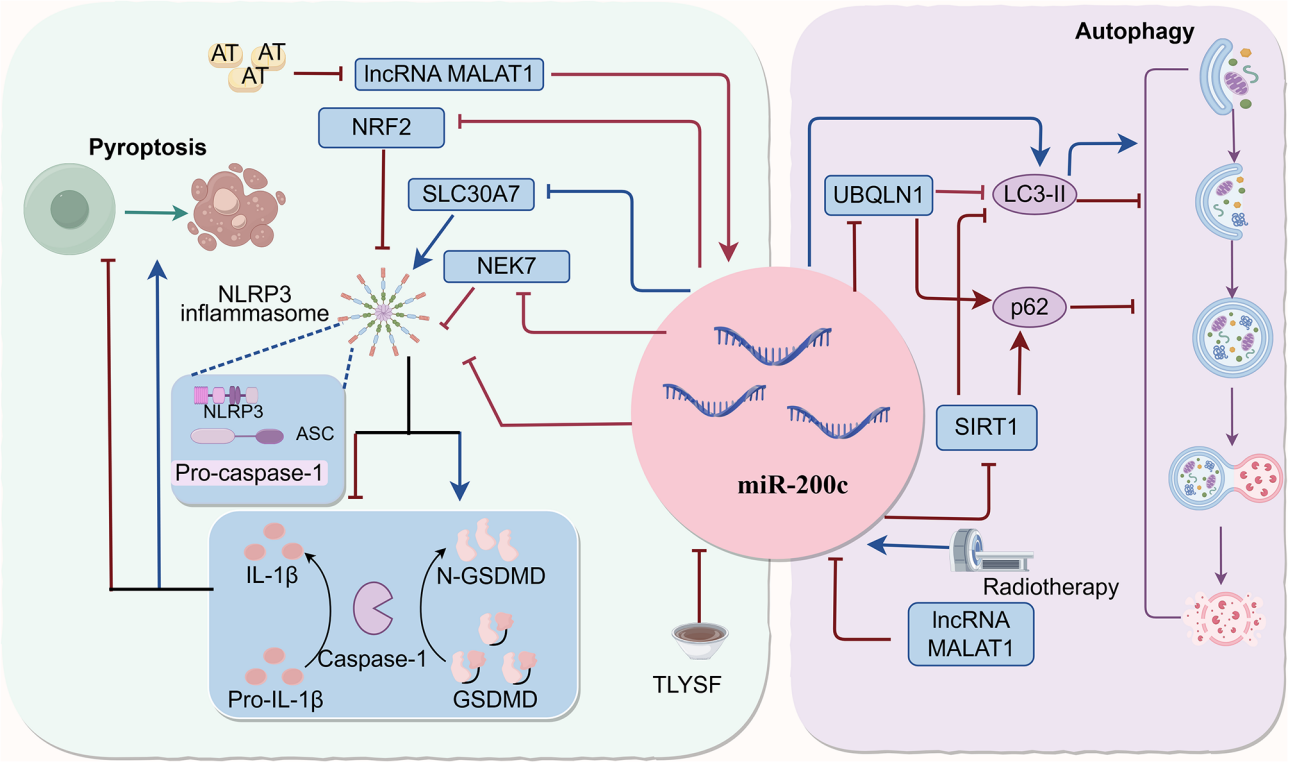

Figure 4. Molecular mechanisms through which miR-200c regulates autophagy and pyroptosis. Blue lines indicate positive regulatory pathways, while red lines indicate negative regulatory pathways. Arrows indicate promotion (→) or inhibition (⊣) (figure generated with figdraw). miR, microRNA; lncRNA, long non-coding RNA; GSDMD, gasdermin D; NLRP3, NLR family pyrin domain-containing protein 3; ASC, apoptosis-associated speck-like protein.

decreased LC3-II expression, increased p62 expression, and ultimately impaired autophagy. This impairment exacerbates cell death and worsens cerebral ischemic injury (102).

Conversely, in glioblastoma and non-small cell LC (NSCLC), combining miR-200c with radiotherapy significantly elevates LC3-II expression and promotes autophagy-mediated tumor cell death, enhancing overall cell death rates. This finding provides a novel mechanistic insight and potential research direction for combination radiotherapy in cancer treatment (103). In summary, miR-200c exerts diverse regulatory effects on pyroptosis and autophagy, with specific roles dependent on cell type and pathological context (Fig. 4). These insights broaden the understanding of miR-200c's complex functions within cell death pathways and hold promise for developing innovative therapeutic strategies.

4. Therapeutic potential of miR-200c

Due to its importance as an apoptosis regulator, miR-200c has become significant as a tool for reversing drug resistance and customizing treatment protocols. The current research involving miR-200c includes four major areas: i) Regulating miR-200c expression by drugs as a means of inducing apoptosis; ii) manipulating miR-200c to affect cancer cells' sensitivity to drugs; iii) designing nano-formulations for delivery of miR-200c; and iv) utilizing miR-200c as a means of targeting TME. Fourth, therapeutic strategies based on reshaping the TME via miR-200c. The following sections describe recent findings and future directions regarding these areas.

Therapeutic modulation of miR-200c expression by drugs. Another mechanism that drugs employ for treatment involves the use of the apoptosis induction effect by adjusting miR-200c concentrations. However, depending on the particular disease and tissues involved, miR-200c can be upregulated or downregulated to achieve desired therapeutic effects (Table II). Therefore, drugs can either increase or decrease miR-200c expression based on the disease type and miR-200c involvement. There are instances where increasing miR-200c leads to better effects. Resveratrol induces apoptosis and helps inhibit tumorigenesis in CRCs due to increased miR-200c expression (104). Similarly, the antitumor activity of metformin in BC is enhanced by increasing miR-200c expression; as a result, AKT2 and BCL2 proteins get inhibited, leading to proapoptotic Bax/BCL2 imbalance (105).

On the contrary, miR-200c may have a role to play in preventing cell death in specific diseases, therefore any therapy would require downregulation of miR-200c to restore cell death, which is necessary for therapeutic effect. According to a study carried out by Lozano-Herrera *et al* (106) coadministration of both naringenin and FEN, along with bisphenol A decreases miR-200c expression, thus overcoming inhibition of PTEN, expression by miR-200c and restoring apoptosis of CRC cells (106). Similarly, atractylenolide I, a phytochemical utilized in traditional Chinese medicine, exerts an anticancer effect by downregulating miR-200c in cancer stem cells (107).

A combination of drugs may covertly affect the regulation of miR-200c, thus enhancing the effect of drug therapy. For example, in PA, bromocriptine combined with artesunate downregulates miR-200c expression, resulting in increased

Table II. Mechanisms of drug action mediated by regulation of miR-200c expression.

First author/s, year	Disease	Therapeutic drug	miR-200c change	Strand specificity (3p/5p)	Verification method	Target gene/Signaling pathway	Apoptosis direction	(Refs.)
Karimi *et al*, 2017	CRC	Resveratrol	↑	-	-	-	Promotion	(104)
Lozano-Herrera *et al*, 2022	CRC	Naringenin and FEN	↓	-	RT-qPCR and bioinformatics analysis	Upregulation of PTEN expression	Promotion	(106)
Tang *et al*, 2020	CRC	Atractylolide I	↓	-	-	-	Promotion	(107)
Zhang *et al*, 2017	BC	Metformin	↑	-	RT-qPCR and western blotting	Targeting and inhibition of AKT2 and BCL2	Promotion	(105)
Wang *et al*, 2017	PA	Bromocriptine and Artesunate	↓	-	RT-qPCR, western blotting and immunocytochemistry	Upregulation of PTEN expression	Promotion	(108)
Chen *et al*, 2013	PA	SZ-685C	↓	-	-	-	Promotion	(109)
Deng *et al*, 2017; Huang *et al*, 2022	MI/RI	Propofol	↓	-3p	Luciferase reporter assay, RT-qPCR and western blotting	Upregulation of AdipoR2 and activation of STAT3 signaling pathway	Inhibition	(110,111)

CRC, colorectal cancer; BC, breast cancer; PA, pituitary adenoma; MI/RI, myocardial ischemia/reperfusion injury; PTEN, phosphatase and tensin homolog; AKT2, AKT serine/threonine kinase 2; BCL2, BCL2 apoptosis regulator; AdipoR2, adiponectin receptor 2; STAT3, signal transducer and activator of transcription 3; RT-qPCR, reverse transcription-quantitative PCR.

PTEN expression and enhanced antitumor effects (108). Furthermore, the marine-derived compound SZ-685C effectively reduces miR-200c levels, induces apoptosis in PA MMQ cells, and increases therapeutic efficacy, presenting a promising targeted treatment approach for PAs (109).

Under the conditions of myocardial ischemia/reperfusion injury (MI/RI), associated with diabetes, reduction of miR-200c leads to anti-apoptotic effects that enhance the chances of successful treatment. Propofol, a cardioprotective agent, exerts its protective effect by suppressing miR-200c-3p, followed by activation of adiponectin receptor 2 and subsequent induction of the STAT3 signaling pathway (110). This contributes to protection against heart muscle cells death and delays progression of MI/RI (111). In summary, it can be deduced that the same signaling pathways can be involved in various types of treatment and lead to diverse effects depending on the pathophysiological condition. This demonstrates the role of miR-200c that is disease-dependent. Hence, the targeting of miR-200c should be adjusted to particular diseases.

miR-200c influences treatment resistance through regulation of apoptosis. Other than being an effector molecule responsible for implementing induced by pharmacotherapy, miR-200c is a regulator of anticancer drug resistance through modulation of apoptosis. Cisplatin (DDP) is the standard anticancer chemotherapy drug, and the role played by miR-200c in modulating sensitivity to DDP has been validated in numerous cancers and proved to be two-fold. For example, in the study by Hamano *et al* (112) on esophageal cancer, the pro-survival function of miR-200c is observed as it activates PPP2R1B and the Akt pathway and thus increases DDP resistance. Conversely, miR-200c enhances DDP sensitivity in GC by specifically targeting RhoE, and in NSCLC by targeting BCL2 and XIAP, thereby promoting apoptosis and reversing DDP resistance (47,113). These differences in miR-200c-mediated effects likely depend on disease-specific downstream target genes.

Apart from DDP, miR-200c is also responsible for altering the resistance towards other treatment approaches. As an instance, miR-200c renders the GC cells sensitive again towards vincristine through downregulation of the two genes, BCL2 and XIAP (47). Similarly, in CCRCC, miR-200c specifically silences the anti-apoptotic protein heme oxygenase 1. This mechanism increases the expression of the pro-apoptotic proteins Bid and Bax and decreases the anti-apoptotic proteins BCL-xL and BCL2, enhancing apoptosis induced by sorafenib and imatinib, thus overcoming drug resistance (114). miR-200c can overcome resistance to chemotherapy in LC. The downregulation of miR-200c is significantly associated with the development of resistance against methotrexate therapy in NSCLC. Upregulating miR-200c enhances the efficacy of methotrexate by modulating the p53/p21 signaling pathway (115). Additionally, Bai *et al* (116) demonstrated that miR-200c upregulates the expression of the pro-apoptotic markers caspase-3 and caspase-9, enhancing the resveratrol-induced apoptotic in LC cells. Resistance to paclitaxel continues to be a significant problem in BC treatment (117). It has been found that regulates miR-200c-3p regulates SOX2 expression in paclitaxel-resistant MCF-7/Tax cells, inducing apoptosis and re-establishing sensitiveness to paclitaxel (118). Additionally, miR-200c mediated reversal of drug resistance in BC is regulated by lncRNAs. The lncRNA XIST acts as a competitive endogenous RNA: Its downregulation reduces ANLN expression, consequently elevating miR-200c-3p, which promotes apoptosis and reverses doxorubicin resistance in MDA-MB-231/ADM cells (119).

Of particular importance is the fact that EMT lies right at the intersection between metastasis and apoptosis resistance (86-88), and as such acts as one of the driving forces behind multidrug resistance, steering therapeutic options in a negative direction (120-122). Numerous cells that go through EMT become resistant to apoptosis, becoming more robust against any type of therapy. miR-200c stands out in this respect as an important inhibitor of EMT by acting as a suppressor of the transcription factors that drive EMT, specifically ZEB1 and ZEB2, thus maintaining the epithelial cell phenotype (8,23,123,124). By inhibiting EMT, miR-200c facilitates apoptosis and restores drug sensitivity in various cancers.

This process has been confirmed for a number of cancers. Specifically, the development of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors' resistance is very common during the treatment of patients with EGFR mutations who are suffering from NSCLC. miR-200c counteracts the development of resistance to the aforementioned inhibitors as a result of EMT suppression, thus leading to an increased level of apoptosis in response to gefitinib and osimertinib (125). Similarly, miR-200c reverses drug resistance by suppressing the process of EMT through targeting of the ZEB family in patients with GC and BC. According to Jiang *et al* (126), miR-200c suppresses DDP resistance through the ZEB2 gene, thus contributing to apoptosis. In BC, miR-200c enhances apoptosis through two distinct pathways: First, by inhibiting ZEB1 and augmenting p53-mediated apoptosis to reverse doxorubicin resistance; second, in doxorubicin-resistant MCF-7 cells, ultrasound-mediated miR-200c overexpression reduces P-glycoprotein expression via ZEB1 inhibition, restoring drug sensitivity (124,127).

In summary, miR-200c significantly influences resistance to multiple chemotherapeutic agents (Table III), highlighting its potential as promising biomarker for predicting chemotherapy resistance. However, current evidence regarding the association between miR-200c and drug resistance is primarily derived from cellular models, with limited clinical data available from *in vivo* studies. Further research is required to confirm whether miR-200c expression levels directly affect therapeutic outcomes in patients.

Therapeutic applications in the TME. miR-200c is a miRNA that acts as an orchestrator within the TME through various means, allowing specific treatments for cancers to be developed. It can change the environment of a tumor through regulation of tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), and the immune checkpoint molecule PD-L1, which contribute to tumor development. The TAMs are immune cells within the TME. A study has shown that breast cancer cells in the process of apoptosis are able to transport the miRNA to macrophages through a CD36 receptor. Inside the macrophages, the miR-200c blocks the genes related to macrophage movement (such as PPM1F and MSN). Thus, there will

Table III. Regulation of drug resistance by microRNA-200c.

First author/s, year	Disease	Therapeutic drug	Strand specificity (3p/5p)	Target gene/signaling pathway	Verification method	Effect on resistance	(Refs.)
Jiang *et al*, 2017	Gastric cancer	Cisplatin	-	Targeted inhibition of ZEB2	Luciferase reporter assays, RT-qPCR, western blotting and bioinformatics analysis	↓	(126)
Ghasabi *et al*, 2019	Gastric cancer	Cisplatin	-	Targeted inhibition of RhoE	RT-qPCR and western blotting	↓	(113)
Zhu *et al*, 2012	Gastric cancer	Vincristine	-	Targeted inhibition of BCL2 and XIAP	Luciferase reporter assay and western blotting	↓	(47)
Hamano *et al*, 2011	Esophageal cancer	Cisplatin	-	Targeted inhibition of PPP2R1B	Luciferase assay, western blotting and bioinformatics analysis	↑	(112)
Bai *et al*, 2014	Lung cancer	Resveratrol	-	-	-	↓	(116)
Zhu *et al*, 2012	Lung cancer	Cisplatin	-	Targeted inhibition of BCL2 and XIAP	Luciferase reporter assay and western blotting	↓	(47)
Gao *et al*, 2014	Clear cell renal cell carcinoma	Sorafenib and imatinib	-	Targeted inhibition of the anti-apoptotic protein HO-1	Luciferase reporter assay, RT-qPCR and western blotting	↓	(114)
Shan *et al*, 2016	Non-small cell lung cancer	Methotrexate	-	Through the p53/p21 pathway	Western blotting	↓	(115)
Wang *et al*, 2020	Non-small cell lung cancer	Gefitinib and osimertinib	-3p	-	-	↓	(125)
Chen *et al*, 2018	Breast cancer	Paclitaxel	-3p	Targeted inhibition of SOX2	Luciferase reporter assay, RT-qPCR and western blotting	↓	(118)
Zhang *et al*, 2020	Breast cancer	Adriamycin (doxorubicin)	-3p	Targeted inhibition of ANLN	Luciferase reporter assays, RT-qPCR and western blotting	↓	(119)
Tryndyak *et al*, 2010	Breast cancer	Doxorubicin	-	Targeted inhibition of ZEB1	RT-qPCR and western blotting	↓	(124)
Huang *et al*, 2018	Breast cancer	Doxorubicin	-	Targeted inhibition of ZEB1	Luciferase reporter assay, RT-qPCR and western blotting	↓	(127)

ZEB2, zinc finger E-box binding homeobox 2; RhoE, Ras homolog family member E; BCL2, B-cell lymphoma 2; XIAP, X-linked inhibitor of apoptosis protein; PPP2R1B, protein phosphatase 2 scaffold subunit Aβ; HO-1, heme oxygenase 1; p53, tumor protein p53; p21, cyclin-dependent kinase inhibitor 1A; SOX2, SRY-box transcription factor 2; ANLN, anillin; ZEB1, zinc finger E-box binding homeobox 1; RT-qPCR, reverse transcription-quantitative PCR.

be fewer infiltrating macrophages within the tumor (128). This demonstrates that miR-200c can modify the TME through intercellular transfer, ultimately affecting tumor progression.

Another stromal factor involved in the TME is the CAFs. Typically, the activation of CAFs results in tumor progression. However, the role of miR-200c in CAFs is distinct from its role in macrophages, although the precise mechanism is yet to be fully elucidated. Typically, the level of miR-200c in CAFs is downregulated (129). As reported by Lin *et al* (130), OS-mediated miR-200c promoter demethylation leads to increased expression of this molecule in CAFs, resulting in mesenchymal-to-epithelial transition reprogramming via COMMD1-NFκB-HIF suppression. Such reprogramming results in increased proliferation and reduced apoptosis of cancer cells while promoting immune suppression and tumor progression (130). PD-L1, an immune checkpoint protein, mediates tumor immune evasion. miR-200c indirectly downregulates PD-L1 by inhibiting ZEB1, thereby reducing immunosuppression of $CD8^+$ T cells, limiting tumor immune evasion, and preventing distant metastasis (131).

miR-200c-based nanotherapies. With the ability to play the significant role of conducting apoptosis, pyroptosis and autophagy, miR-200c is an important element in orchestrating numerous diseases. The more the roles of this element are known and explored, the more miR-200c proves itself to be promising as a potential therapeutic element and has become a worthy drug candidate. However, the way from research and discovery to treatment faces numerous difficulties. Firstly, RNA molecules are quite vulnerable because they can easily degrade when encountering nucleases; besides, their delivery is unpredictable and non-precise.

The current options for delivering miRNA include viral and non-viral techniques. Though the viral vectors exhibit high efficiency in transfection, their safety concerns related to immunogenicity and tumorigenicity limit their medical applications. By contrast, the non-viral delivery systems pose little immunogenicity and are highly biocompatible, thus serving as main candidates for miR-200c delivery. The list of non-viral techniques involves the following: Inorganic nanoparticles, polymeric nanocarriers, lipid vesicles, exosomes and liposomes (132). As for nano-delivery approaches, they proved particularly encouraging when developing miR-200c-based drugs.

Qian *et al* (133) developed miR-200c-loaded nanoparticles, effectively delivered them into AGS GC cells, and enhanced apoptosis in combination with radiotherapy, significantly improving therapeutic efficacy. In BC therapy, Garrido-Cano *et al* (134) utilized mesoporous silica nanoparticles to deliver miR-200c-3p into MDA-MB-231 cells, effectively downregulating ZEB1 and ZEB2, thereby inhibiting EMT and achieving potent anticancer effects. Nano-delivery approaches also exhibit significant potential in OA. Zheng *et al* (135) prepared a lipo-AgPEI-miR-200c-3p complex using a microfluidic device to encapsulate miR-200c-3p into silver nitrate-polyethyleneimine nanoparticles. They successfully delivered miR-200c-3p into chondrocytes, significantly reduced apoptosis by downregulating Bax and cleaved caspase-3, and increased BCL2 expression, providing a novel approach for OA treatment.

Even with the potential benefits associated with it, developing a nanoparticle-based therapy for use in humans presents challenges that make this pathway a rather congested one. Once they enter the body through a systemic route, nanoparticles are rapidly absorbed into the body's immune system, reducing their availability in the target tissue to an enormous degree. Since miR-200c has wide-ranging effects on gene expression, it increases the risk of non-specific effects if it enters other non-target cells after delivery. Modifications made to miRNA to maintain stability in blood can reduce its effectiveness within cells. More importantly, the context-dependent nature of miR-200c's function poses unique safety challenges: i) miR-200c is involved in normal physiological processes such as wound healing, cardiac development and embryonic development; systemic administration may interfere with these normal physiological functions; ii) exogenous miRNAs and their delivery vehicles are recognized by the immune system, triggering an immune response and inflammatory reaction; and iii) nanoparticles are captured by hepatic macrophages, leading to their accumulation in the liver; this off-target accumulation may result in hepatocyte damage, elevated transaminases and abnormal liver function, and the hepatotoxic consequences of long-term accumulation remain unclear (136,137).

Nano-delivery approaches can be considered as one of the feasible options to protect miR-200c from instability and degradation. While there is a lot of potential in the development of miR-200c-based nanotherapeutics, various issues need to be addressed, such as improving efficacy of delivery, limiting adverse side effects, decreasing the risk of immunological response, and proving that chemically modified miRNAs are safe for humans. Further efforts must address all of the aforementioned concerns and assess safety in animal studies, which would enhance the effectiveness of therapy.

5. Conclusion

miR-200c plays an essential role in cell life because it regulates the processes of apoptosis, autophagy and pyroptosis through various molecular pathways. When the organism is healthy, it maintains the harmony of epithelial tissues and promotes important developmental events (for example, teeth and cardiac formation), regulating pluripotency vs. differentiation in ESCs. When the organism suffers from disease, miR-200c controls the cell's fate by acting on several targets and signaling pathways. It directly affects apoptosis by silencing genes that regulate the process or indirectly through AKT pathway. At the same time, miR-200c also integrates itself in autophagy and pyroptosis, resulting in a complicated regulation system for cellular decisions to live or die.

Specifically, miR-200c can be regarded as an excellent candidate for developing new therapeutic interventions, considering its sensitivity to medication therapy and capability to regulate drug resistance in various diseases. However, the application of drugs that are based on miR-200c requires additional validation to be used in clinical practice. Although preclinical trials have demonstrated positive outcomes of the targeted delivery of miR-200c into a particular location, a lot of research remains to be conducted regarding delivering the substance efficiently and accurately. Specifically, three crucial

problems should be addressed by future research, namely: i) Tissue and cellular targeting to reduce possible negative effects of the off-target delivery of the substance; ii) ensuring safety and efficiency of the therapy; and iii) maintaining miR-200c stability and activity *in vivo*.

Furthermore, future studies need to elucidate the mechanism by which miR-200c regulates apoptosis, autophagy and pyroptosis collectively in one disease context. Currently, the focus is on exploring these cell death pathways individually using various diseases as their context, thus making it unknown whether miR-200c regulates all the three types of cell deaths together in one disease context. It is only by focusing on one particular model that it will be possible to determine whether miR-200c acts as a master regulator.

Complete investigations into how miR-200c acts in different ways according to the disease stage and type of cells involved will result in exact windows of therapeutic opportunities being defined, thus leading to the development of miR-200c-based therapies for clinical applications. This progress would not only transform miR-200c a practical therapeutic tool but also deepen our understanding of programmed cell death regulation, offering new insights and strategies for disease diagnosis and treatment.

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Availability of data and materials

Not applicable.

Authors' contributions

XW and HD were responsible for manuscript writing, and conceived and designed the study. YS and XW were responsible for the collection and assembly of data. YS and HD were responsible for data analysis and interpretation. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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