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To be or not to be: navigating the influence of MicroRNAs on cervical cancer cell death

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Abstract

With all diagnostic and therapeutic advances, such as surgery, radiation- and chemo-therapy, cervical cancer (CC) is still ranked fourth among the most frequent cancers in women globally. New biomarkers and therapeutic targets are warranted to be discovered for the early detection, treatment, and prognosis of CC. As component of the non-coding RNA's family, microRNAs (miRNAs) participate in several cellular functions such as cell proliferation, gene expression, many signaling cascades, apoptosis, angiogenesis, etc. MiRNAs can suppress or induce programmed cell death (PCD) pathways by altering their regulatory genes. Besides, abnormal expression of miRNAs weakens or promotes various signaling pathways associated with PCD, resulting in the development of human diseases such as CC. For that reason, understanding the effects that miRNAs exert on the various modes of tumor PCD, and evaluating the potential of miRNAs to serve as targets for induction of cell death and reappearance of chemotherapy. The current study aims to define the effect that miRNAs exert on cell apoptosis, autophagy, pyroptosis, ferroptosis, and anoikis in cervical cancer to investigate possible targets for cervical cancer therapy. Manipulating the PCD pathways by miRNAs could be considered a primary therapeutic strategy for cervical cancer.

Keywords Cervical cancer, MicroRNAs, Apoptosis, Ferroptosis, Pyroptosis, Autophagy

Introduction

Cervical cancer (CC), a frequent female malignancy, possesses a high rate of mortality worldwide and is considered a major global health challenge [1, 2]. Adenocarcinoma and squamous cell carcinoma, respectively generate 25% and 70% of all CCs and are the most common histological subtypes [3, 4]. Several factors and genes are implicated in generating the molecular regulatory mechanism of CC [5, 6].

Additionally, high-risk subtypes of the human papillomavirus (HPV) are known to be responsible for most CCs. Considering the major contribution of this virus, HPV screening and vaccination programs are identified as effective strategies in the prevention of CC [7]. In the context of treatment, it should be noted that surgical resection is still the foremost treatment option for early-stage CCs due to its acceptable prognosis [5, 6]. However,

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the diagnosis and treatment platform for CC are not specified for monitoring the prognosis, tumor metastasis, and recurrence, thereby lacking individualized treatment.

Through eliminating damaged cells, cell death takes a fundamental role in the maintenance of physiological homeostasis and can appear as an aberrant pathological response to damaging stimuli [8, 9]. In accordance with morphology, biochemistry, and function, cell death modes are divided into accidental cell death and regulated cell death (RCD) [10]. As the name suggests, accidental cell death is an uncontrolled biological process in reaction to accidental injury stimuli [11]. Despite this, RCD is characterized by regulated signaling cascades with critical roles in the development of organisms or tissue renewal [12]. Malignant cells, however, are capable of evading the RCD routes through various mechanisms [13]. RCD pathways are pivotal for cancer immune surveillance, progression, metastasis, and the prognosis of patients [14, 15]. Different forms of RCD could alter the tumor microenvironment through the release of pathogen- or damage-associated molecular patterns (PAMPs or DAMPs), which impacts anti-cancer therapy [16–18]. Therefore, more investigations are a must for a more comprehensive understanding of the implication of cell death pathways in cancer therapy and development.

MiRNAs are small, non-coding RNAs capable of binding to the target mRNAs and, altering the translation of the target proteins, or even degrading the mRNA [19–21]. Various cellular processes, like metabolism, proliferation, and cell death, in distinct types of cells are modulated by miRNAs [19, 22, 23]. Abnormal expression of miRNAs weakens or modifies various RCD, leading to human cancer development. As well, several miRNAs are identified to alter the expression of RCD genes [24, 25]. Aberrations involving miRNAs involved in apoptosis, autophagy, pyroptosis, ferroptosis, anoikis, and necroptosis can also influence the physiological conditions and affect carcinogenesis. The present study contains a review of the significant role of miRNAs in controlling the critical cell death pathways, namely, apoptosis, autophagy, pyroptosis, anoikis and ferroptosis of cervical cancer cells.

MicroRNA biogenesis

During canonical biogenesis, RNA polymerase II transcribes miRNAs and produces a double-stranded hairpin primary (pri)-miRNA transcript, which are further cleaved into a short hairpin structure known as pre-miRNA. After translocation of pre-miRNA to the cytoplasm, their terminal loop gets removed by the RNase III endonuclease Dicer and leaves a mature miRNA duplex strands [26]. Either strand of mature miRNA (– 5p or – 3p) can be loaded onto the Argonaute protein to generate the RNA-induced silencing complex (RISC). The strand with more thermodynamical stability will be proportioned in RISC while the less stable strand will be degraded [27]. The proportion of strands can also be equal or dependent on the cell type. Besides, according to the functionality of proportion of the strands (– 5p or – 3p), RISC could be directed towards divergent gene targets [28, 29]. Next, through attaching to the 3'-UTR of target mRNA, miRNAs affect gene expression, either by translational repression or even degradation, resulting in the regulation of various cellular processes and disease progression. Moreover, both miRNAs and pre-miRNAs are stable in extracellular environment and can be released into the bloodstream in free form or in exosomes, microvesicles, high-density lipoproteins or protein complexes, where they are adsorbed by cell-to-cell communication [30]. Therefore, they are considered therapeutic targets and clinical biomarkers for individualized therapy in complex diseases [31–35].

Apoptotic and anti-apoptotic MicroRNAs in cervical Cancer

Among the different types of RCD, apoptosis and autophagy are the most pivotal ones with the ability to promote organelle degradation or stress-induced cell death and serve a critical role in targeted therapy as well as regulating cancer cell death [36]. Apoptosis is identified as a crucial intracellular process for maintaining organism homeostasis and controlling cell populations. Various morphological features of apoptosis such as shrinkage of cell, condensation of chromatin, blebbing of the membrane, DNA fragmentation, and the formation of apoptotic bodies [37–39].

Depending on the activation, apoptosis is categorized into two modes; intrinsic and extrinsic pathways. The intrinsic pathway activates once stressed cells produce an internal signal and relies on the cytoplasmic release of cytochrome C into the mitochondrial intermembrane space (MIS), through the mitochondrial outer membrane (MOM) pores. BCL-2 family proteins are the main regulators and effectors of the permeabilization of MOM, resulting in the release of cytochrome C from the MIS [40]. BCL-2 family members are categorized as effectors (including BAX and BAK), the pro-apoptotic BH3-only (e.g., Bad, Bid, Bik, and Bim) and anti-apoptotic proteins (Bcl-2, Bcl-xL, Bcl-w, Mcl-1, and A1) [40, 41]. Through the release of cytochrome C from MOM into the cytosol, BCL-2 members trigger the activation of caspase cascade, leading to apoptosis [42]. In the extrinsic pathway, on the other hand, the activation of receptors through members of the tumor necrosis factor (TNF) receptors (e.g., FAS) and TNF-related apoptosis inducing ligand (TRAIL) receptors, is required. Binding of death ligands (TNFα, FAS, and TRAIL) to their receptors activates the extrinsic pathway and further result in recruitment of caspase9/10

and, thereby the formation of a death-inducing signaling complex (DISC) [42]. Afterward caspase9/10 activated by autocleavage in the DISC, triggers the activation of downstream executioner caspases (caspase3/6/7) (Fig. 1) [43, 44].

Caspases, a group of proteases, are mostly identified by their role in PCD (mostly apoptosis and pyroptosis), and the inflammatory cascade. Caspase3/6/7/8/9 in mammals are known as apoptotic caspases, whereas caspase1/4/5/12 in humans and caspase1/11/12 in mice are considered as inflammatory caspases [45]. Furthermore, apoptotic caspases are classified into initiator caspases (caspase-8/9) and executioner caspases (caspase3/6/7) based on their mechanism of action [46–48].

All, PCD pathways such as apoptosis, autophagy, pyroptosis, ferroptosis, and necroptosis appear to get regulated by various miRNAs. In that regard, within the next section, we summarize the mechanism of inhibiting or inducing apoptosis in cervical cancer by cellular miRNAs.

Apoptotic MicroRNAs in cervical cancer

In critical biological and pathological processes, miRNAs are found to be crucial regulators [19, 21, 45, 46]. Considering the pivotal part of miRNAs in the regulatory network, any changes in their expression are correlated with tumor progression. In that context, many researches have been centered on the participation of miRNAs to the carcinogenesis and progression of CC [47–50]. For instance, the role of miR-218 as an apoptosis regulator and suppressor of progression has been investigated in CC [51–53]. Yu et al. [54] reported that the expression level of survivin and miR-218 are downregulated and upregulated, respectively, in cisplatin (DDP)-resistant HeLa/DDP and SiHa/DDP cells in contrast to the mock HeLa and SiHa cells. In return, enforced expression of miR-218 elevates the cisplatin sensitivity of CC cells by promoting apoptosis. As well, induction of miR-218 is found to promote apoptosis in CC cells' resistance to DDP by targeting survivin [54]. In that regard, Yuan et al. [55] found that enforcing the expression of miR-218 elevated the radiosensitivity in CC cells, including HeLa, SiHa, C33A, and CaSki cells by promoting apoptosis [55]. Similarly, another study demonstrated that miR-218 increases chemosensitivity to DDP in Hela cells via promoting CC cell apoptosis [56]. Zhu et al. observed that miR-218 overexpression suppresses cell viability and elevates apoptosis in CC cells via the JAK2/STAT3 pathway [57]. GLI3, in the GLI family, affects proliferation and apoptosis in cancer cells [58–60]. Recently, it has been observed that Gli3 mRNA and protein expression are inversely associated with levels of miR-218 in CC tissues

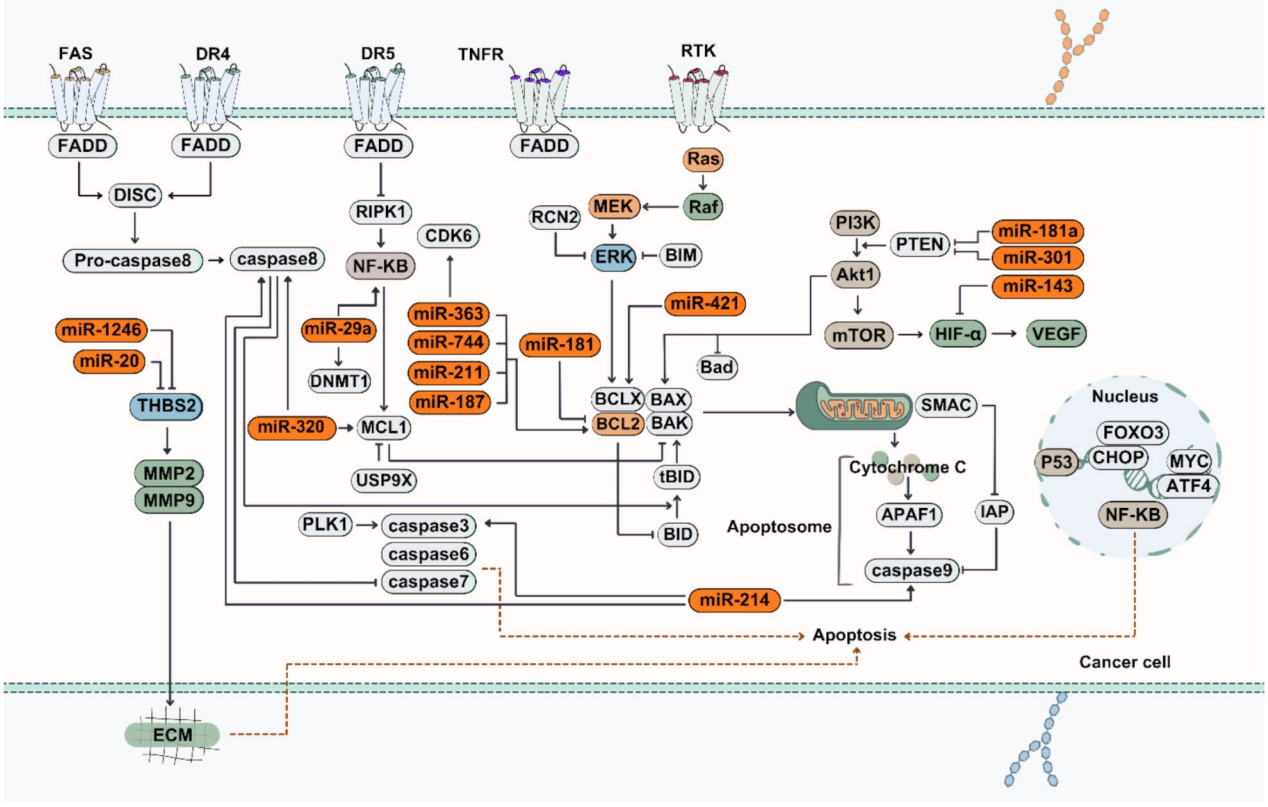

Fig. 1 Cancer cell apoptosis and regulatory non-coding RNAs. Regulatory microRNAs are highlighted in orange

[61]. In addition, miR-218 is found as a suppressor of CC cells proliferation, apoptosis, and cell cycle progression of through downregulating Gli3. It also has been established that transfection of miR-218 mimics in CC cells results in promoted apoptosis and enhanced caspase-3 activity [61]. These results suggested that miR-218 can suppress cell growth and regulate tumor progression through elevating the activity of caspase-3 and inducing apoptosis in CC cells.

The phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) cascade, is a critical signaling cascade which involved in regulating apoptosis, and blocks the expression of pro-apoptotic proteins, suppresses tissue apoptosis, and elevates the survival rate of cancerous cells [62]. Focal adhesion kinase (FAK) is a signaling molecule identified to activate PI3K [63, 64]. In fact, FAK participates in the cell survival regulation and protection from apoptosis [65–67]. It has also been established that FAK suppresses cell apoptosis through triggering the PI3K/Akt cascade [68, 69]. Phosphorylation of FAK occurs upon stimulation and enables it to attach to the p85 subunit of PI3K and consequently triggers the PI3K/Akt signal cascade. Furthermore, activation of FAK-PI3K/Akt pathway participates in the protection of cancer cells from oxidative stress-induced apoptosis through promoting nuclear factor-κB (NF-κB) to mediate the expression of caspase inhibitors of IAPs [66]. Similar to FAK, MTDH serves a crucial role in various biological processes in tumorigenesis and development through integrating oncogenic cascades, such as PI3K/AKT, NF-κB, mitogen-activated protein kinase (MAPK), and Wnt/β-catenin [70, 71]. Overexpression of MTDH suppresses apoptosis, and in return, downregulation of MTDH is able to reduce tumor cell growth, and promote apoptosis [72, 73]. In CC, MTDH is overexpressed and has a remarkable association with tumor size, lymph node metastasis, TNM stage, and tumor differentiation [74, 75]. Liang et al. [76] found that upregulated miR-433 induces CC apoptosis and suppresses proliferation and invasion by targeting MTDH. Additionally, upregulated MTDH mRNA expression in CC tissues has an inverse association with miR-433 expression. Overexpression of MTDH is able to reverse the influence of upregulated miR-433 in regard to proliferation, invasion, and apoptosis of CC cells. Moreover, miR-433 is found to inactivate AKT and β-catenin pathways in CC via targeting MTDH [76]. Collectively, these data indicate that miR-433 suppressed the growth of CC cells via the promoting apoptosis pathway by modulating the FAK-MTDH/PI3K/AKT signaling cascade.

Furthermore, BCL-2 protein is found to inhibit apoptosis through the formation of a heterodimer with BAX and guarantee cell survival by controlling the Ca^{2t} concentration and antioxidant effect [77]. BCL-2 is also able to suppress the activities of caspase-9/3/6/7 [78], in order to eliminate apoptosis, elongate the survival time of tumor cells, and create malignant cell transformation [79]. Recent evidence supports that miRNAs act as tumor suppressor factors in CC through promoting apoptosis pathways via targeting Bcl-2 (Table 1). For example, Chen and colleagues [84] found that miR-744 negatively regulates Bcl-2 and subsequently suppresses CC growth and progression through promoting apoptosis [80]. Enforced miR-211 expression, on the other hand, promotes apoptosis in CC cells (SiHa cells) by targeting Bcl-2 and upregulating apoptotic proteins, such as caspase-3, and PARP [81]. Similarly, He et al. [82] reported that miR-187 promotes apoptosis of SiHa CC cells by suppressing the expression of Bcl-2 [82]. Moreover, miR-636 is found to be downregulated in CC tissues and cell lines. Overexpression of miR-636 results in suppressed cell proliferation and elevated cell apoptosis. Knockdown of miR-636, on the other hand, is capable of reversing these effects on CC tumorigenesis. In addition to Bcl-2, mir-636 is found to target cyclin-dependent kinase 6 (CDK6) and upregulation of CDK6 or Bcl-2 might reverse the inhibitory effect of miR-636 on the progression of CC. Therefore, CDK6/Bcl-2 are considered targets of miR-636 for promoting CC cell [83]. Bcl2l2 (also known as Bcl-w), was initially classified among BCL-2 family proteins, and it's overexpression was found to shield lymphoid and myeloid cells from cytokine deprivation and γ-irradiation-induced apoptosis [84].

Through apoptosis protection of cells and promotion of cell survival, Bcl2l2 participates in chemoresistance [84–87]. In fact, Bcl2l2 is overexpressed in various cancer types to promote their carcinogenesis, for instance, non-small cell lung cancer [88], gastric and colon cancers [89, 90]. Wang et al. [91] established that upregulated Bcl2l2 in CC tissues promotes cell survival and cisplatin resistance. Furthermore, they confirmed that through the direct attachment of miR-214 to the 3´ UTR of Bcl2l2 mRNA, it can suppress Bcl2l2 at the post-transcriptional level. Moreover, they suggested that enforced expression of miR-214 in HeLa cells could upregulate Bax as well as caspase-9/8/3, which were partly reversed through upregulation of Bcl2l2. This indicates that both extrinsic and intrinsic pathways are implicated in miR-214-induced apoptosis [91].

With a similar structure to the BCL-2 gene, the BCL-XL, is a MOM and nuclear membrane protein capable of binding to nuclear proteins and regulating the activity of transcription factors [31]. BCL-XL has higher expression in tumor cells in contrast to standard cells, and is associated with the proliferation, growth, metastasis, apoptosis resistance and maintenance of stem cell phenotypic of tumor cells [92, 93]. A high expression level of Bcl-xL has been reported in CC cells (c-33a cells) and miR-421-transfected c-33a cells exhibit reduced

Table 1 Apoptotic MicroRNA in cervical cancer cells

MicroRNA (Expression)	Target	Samples	Note	Ref
MiR-1258 (Down)	E2F1	In Vitro (c-33 A cells cells), In vivo (mice)	MiR-1258 promotes CC apoptosis by targeting E2F1.	[237]
miR-519d-3p	HIF-2α	In vitro (HeLa cells)	MiR-519d-3p enhances the apoptosis of CC under hypoxia condition by targeting HIF-2α.	[238]
miR-143 (Down)	HIF-1α	Human (cervical cancer tissues), In vitro (HeLa cells)	Ectopic expression of miR-143 increases apoptosis rate of CC cells by targeting HIF-1α.	[112]
miR-143 (Down)	-	In vitro (CaSki cells)	MiR-143 promotes the apoptosis rate in cisplatin resistance CC cells	[239]
miR-18a	ATM	In vitro (SiHa and HeLa cells)	MiR-18a enhances the radiation-induced apoptosis in CC cells by targeting ATM.	[240]
miR-218	-	In vitro (HeLa cells)	Overexpressed miR-218 promotes the radiation-induced apoptosis in CC cells.	[55]
miR-218	Survivin	In vitro (SiHa/DDP and HeLa/DDP cells)	Overexpresses miR-218 induces cisplatin-resistance cervical cancer cells by targeting	[241]
miR-218 (Down)	Gli3	Human (CC tissues), In vitro (Siha cells)	MiR-218 promotes the apoptosis of cervical CC by targeting Gli3.	[61]
miR-218	-	In vitro (HeLa iha cells)	MiR-218 aggravates sensitivity of HeLa cells to cisplatin by increasing apoptosis through regulating AKT/mTOR pathway.	[56]
miR-218 (Down)	IDO1	Human (cervical cancer tissues), In vitro (HeLa cells)	MiR-218 induces CC cells by targeting IDO1.	[57]
miR-802 (Down)	SRSF9	Human (CC tissues), In vitro (SiHa and HeLa cells)	MiR-802 induces CC apoptosis by targeting SRSF9.	[242]
miR-182 (Down)	DNMT3a	Human (CC tissues), In vitro (C4-II cells)	MiR-182 enhances CC cell apoptosis by targeting DNMT3a.	[243]
miR-34b (Down)	-	Human (CC tissues), In vitro (C33a cells)	MiR-34b induces the apoptosis of CC cells.	[244]
miR-34a-5p	Bcl-2	In vitro (HeLa cells)	Upregulated miR-34a-5p induces CC apoptosis by negatively regulating Bcl-2 levels.	
miR-503-5p (Down)	-	In vitro (SiHa and HeLa cells)	LINC00460 inhibits the CC cell apoptosis by sponging miR-503-5p.	[246]
miR-15a-5p (Down)	YAP1	Human (CC tissues), In vitro (SiHa and C-33 A cells)	MiR-15a-5p enhances the apoptosis of CC by negatively regulating YAP1.	[246]
miR-125b	PIK3CD	In vitro (HeLa cells)	MiR-125b induces apoptosis of CC by negatively regulating PIK3CD.	[247]
miR-744 (Down)	Bcl-2	Human (CC tissues), In vitro (SiHa and C4-1 cells)	MiR-744 promotes CC cells by negatively regulating Bcl-2.	[80]
miR-211	Bcl-2	Human (CC tissues), In vitro (SiHa and C-33 A cells)	MiR-211 promotes the autophagy and autophagy dependent apoptosis by targeting Bcl-2.	[81]
miR-636 (Down)	Bcl-2, CDK6	Human (CC tissues), In vitro (CASKI cells)	MiR-636 induces the apoptosis of CC cells by positively regulating Bax and cleaved caspase-3 levels and negatively regulating Bcl-2 levels.	[83]
miR-187	Bcl-2	In vitro (SiHa cells)	MiR-187 induces the apoptosis of CC cells by negatively regulating Bcl-2.	[82]
miR-143 (Down)	Bcl-2	Human (CC tissues), In vitro (HeLa cells)	MiR-143 enhances the apoptosis of CC cells by decreasing the expression level of Bcl-2.	[105]
miR-143 (Down)	Bcl-2	Human (CC tissues), In vitro (SiHa and HeLa cells)	MiR-143 promotes the CC cells by targeting Bcl-2.	[113]
miR-214 (Down)	Bcl2l2	Human (CC tissues), In vitro (C-33 A and HeLa cells)	MiR-214 enhances the apoptosis and cytotoxicity of cisplatin in cancer cells by targeting Bcl2l2.	[91]
miR-421	Bcl-xL	In vitro (c-33a cells)	MiR-421 enhances the apoptosis of CC cells by negatively and positively regulating the expression level of Bcl-xL and caspase-3, respectively.	[248]
miR-7 (Down)	XIAP	Human (CC tissues), In vitro (HeLa and C-33 A cells)	MiR-7 induces CC apoptosis by negatively regulating XIAP levels.	[249]
miR-320	Mcl-1	In vitro (HeLa cells)	MiR-320 induces CC cell apoptosis by negatively and positively regulating Mcl-1 and capspase-3, respectively.	[95]
miR-433 (Down)	FAK	Human (CC tissues), In vitro (CaSki cells)	MiR-433 enhances CC apoptosis by negatively regulating FAK/PI3K/AKT signaling pathway.	[250]
miR-433 (Down)	MTDH	Human (CC tissues), In vitro (SiHa and HeLa cells)	Overexpressed miR-433 leads to the induction of CC cells apoptosis by targeting MTDH.	[76]

Table 1 (continued)

MicroRNA (Expression)	Target	Samples	Note	Ref
miR-374b	JAM-2	In vitro (Siha cells)	MiR-374b induces CC cell apoptosis by negatively regulating p38/ERK pathway through targeting JAM-2.	[251]
miR-101	-	In vitro (SiHa cells)	MiR-101 induces the apoptosis of SiHa cells maybe by negatively regulating COX-2.	[252]
miR-101	-	In vitro (HeLa cells)	MiR-101 promotes the apoptosis of HeLa cells maybe by decreasing the expression level of COX-2.	[253]
miR-140-3p (Down)	RRM2	Human (CC tissues), In vitro (Siha cells)	MiR-140-3p enhances early apoptosis by positively regulating Bax and Cleaved caspase-3 expression levels and negatively regulating Bcl-2 levels through targeting RRM2	[255]
miR-140-5p (Down)	ORC1	Human (CC tissues), In vitro (C33A and HeLa cells)	MiR-140-5p aggravates the apoptosis rate of CC cells by decreasing Bcl-2 and increasing the accumulation of c-caspase3 and cleaved PARP.	[255]
miR-17-5p	TP53INP1	In vitro (C33A and HeLa cells)	Overexpressed miR-17-5p induces CC cells apoptosis by targeting TP53INP1.	[256]
miR-148b (Down)	-	In vitro (HeLa cells)	Ectopic expression of miR-148b induces the apoptosis of CC cells by regulating caspase-3-dependent manner.	[257]
miR-200b	RhoA	In vitro (HeLa cells)	MiR-200b induces the apoptosis of CC cells by targeting RhoA.	[258]
miR-628–5p (Down)	VEGF	Human (CC tissues), In vitro (HeLa cells)	MiR-628–5p enhances the apoptosis of CC cells by negatively regulating VEGF.	[259]
miR-708 (Down)	Timeless	Human (CC tissues), In vitro (SiHa cells)	MiR-708 aggravates the chemo- sensitivity of CC cells by enhancing apoptosis through	[260]
miR-29a	-	In vitro (CaSki and C33A Cells)	miR-29a triggers the apoptosis of radio-resistance CC cells.	[261]
miR-29a (Down)	DNMT1	Human (CC tissues), In vitro (SiHa and HeLa cells)	MiR-29a induces the apoptosis of CC cells by targeting DNMT1 and inactivation of NF-κB pathway.	[262]
miR-497	IGF-1R	In vitro (HeLa and SiHa cells)	MiR-497 aggregates the apoptosis rate of CC cells by positively regulating caspase-3 activity.	[263]
miR-204 (Down)	ATF2	Human (CC tissues), In vitro (C33A cells)	MiR-204 promotes apoptosis and inhibits autophagy by targeting ATF2 in C33A cells.	[160]
miR-940	-	In vitro (Hela cells)	Upregulated miR-940 induces CC cell apoptosis by regulating PI3K/AKT pathway.	
miR-143	-	In vitro (Hela cells)	Upregulated miR-143 mediated by 5-Aminolevulinic acid photodynamic therapy (ALA-PDT) method leads to induction of CC cells apoptosis by negatively and positively regulating Bcl-2 and Bax levels.	[264]
miR-26a-5p (Down)	HSDL2	Human (CC tissues), In vitro (Hela and C33A cells)	Upregulated miR-26a-5p induces the apoptosis of Hela and C33A cells by targeting HSDL2.	[265]
miR-130b-5p	ELK1	In vitro (Hela cells), In vivo (Mice)	Overexpressed miR-130b-5p induces CC cells apoptosis by negatively regulating ELK1.	[266]
miR-612	NOB1	In vitro (SiHa cell)	Enforced expression of miR-612 leads to induction of SiHa cell apoptosis by targeting NOB1.	[267]
miR-375	IGF-1R	In vitro (Caski cells)	Ectopic expression of miR-375 induces apoptosis of Caski cells by targeting IGF-1R.	[268]
miR-139-3p	NOB1	In vitro (Hela cells)	MiR-139-3p enhances the cervical cancer cells by targeting NOB1.	[269]
miR-338-3p (Down)	MACC1	Human (CC tissues), In vitro (Hela cells)	MiR-338-3p accelerates the apoptosis of CC cells by negatively regulating MACC1/MAPK pathway.	[270]
miR-337-3p	Rap1A	Human (CC tissues), In vitro (Hela cells)	MiR-337-3p can induce the apoptosis of CC cells maybe by targeting Rap1A.	[271]
miR-186 (Down)	Kazrin F	Human (CC tissues), In vitro (C33A and HeLa cells)	MiR-186 accelerates the apoptosis of CC cells by inhibiting Kazrin F.	[272]
miR-873-5p (Down)	-	Human (CC tissues), In vitro (SiHa and HeLa cells)	Upregulated miR-873-5p enhances CC apoptosis maybe by targeting ZEB1.	[273]
miR-425	RAB2B	Human (CC tissues), In vitro (DoTc2 cells)	MiR-425 accelerates the apoptosis of CC cells by targeting RAB2B.	[274]
miR-634	mTOR	In vitro (SiHa and HeLa cells)	MiR-634 induces the apoptosis of CC cells by negatively regulating mTOR signaling pathway.	[275]
miR-99a-5p	RRAGD	Human (CC tissues), In vitro (HeLa, SiHa and C33A cells)	MiR-99a-5p induces apoptosis of CC cells by targeting RRAGD.	[276]
miR-181 (Down)	Yin Yang 1	Human (CC tissues), In vitro (HeLa cells)	Upregulated miR-181 enhances the CC apoptosis by targeting Yin Yang 1.	[233]

Table 1 (continued)

MicroRNA (Expression)	Target	Samples	Note	Ref
miR-145 (Down)	HLTF	In vitro (SiHa and HeLa cells)	miR-145 accelerates apoptosis-induced radiotherapy in CC cells.	[277]
miR-145	OCT4	In vitro (Tera cells)	Upregulated miR-145 can aggravates sensitivity of CC cells to low-dose irradiation by increasing the apoptosis rate through targeting OCT4.	[278]
miR-302b-3p, miR-302c-3p or miR-302d-3p	CCNO	In vitro (CasKi cells)	MiR-302b/c/d-3p aggravates the apoptosis of cervical squamous cell carcinoma by targeting CCNO.	[279]
miR-543 (Down)	TRPM7	Human (CC tissues), In vitro (SiHa and HeLa cells)	MiR-543 enhances SiHa and HeLa cells apoptosis by targeting TRPM7.	[280]
miR-100	PLK1	In vitro (Caski and Siha cells)	Overexpressed miR-100 promotes CC cell apoptosis by targeting	[281]
miR-129-5p	SP1	In vitro (HeLa cells)	Ectopic expression of miR-129-5p leads to apoptosis induction in HeLa cells by targeting SP1.	[282]
miR-214 (Down)	FOXM1	Human (CC tissues), In vitro (C33A and HeLa cells)	MiR-214 aggravates CC cells sensitivity to cisplatin by suppressing apoptosis through FOXM1.	[283]
Let-7a (Down)	TGFBR1	Human (CC tissues), In vitro (HeLa cells)	Upregulated let-7a can promote the apoptosis of HeLa cells maybe by targeting TGFBR1.	[284]
miR-3929	Cripto-1	In vitro (HeLa cells), In vivo (mice with HeLa xenograft tumors)	MiR-3929 promotes CC cells apoptosis by targeting Cripto-1.	[285]
miR-1284 (Down)	HMGB1	Human (CC tissues), In vitro (HeLa and SiHa cells)	Upregulated miR-1284 enhances the apoptosis of CC cells by targeting HMGB1.	[286]
miR-504	-	In vitro (SiHa cells)	Upregulated miR-504 promotes the SiHa cell apoptosis and, in return, HPV E6 protein inhibits SiHa cells apoptosis by decreasing miR-504 expression levels.	[287]
miR-22 (Down)	HDAC6	Human (CC tissues), In vitro (HeLa and C33A cells)	Enforcing expression level of miR-22 leads to inducing apoptosis CC cells by targeting HDAC6.	[288]
miR-509-3p	RAC1	In vitro (C-33 A and HCC94 cells)	MiR-509-3p induces CC cells apoptosis by targeting RAC1.	[289]

Bcl-xL expression, suppressed growth, promoted apoptosis, and activated caspase-3. In addition, among BCL2 family members, MCL1 inhibits the apoptosis pathway through the inhibition of BAX and BAK activation [94]. It has been demonstrated that miR-320 induces HeLa cell apoptosis by negatively and positively regulating Mcl-1 and caspase-3, respectively (Fig. 1) [95]. Overall, because apoptosis suppression is pivotal in cancer development and constitutes a main barrier for effective therapy, the research on miRNAs targeting multiple Bcl-2 family members could serve as a promising target for CC treatment.

Radiation triggers the activation of several survival and death signaling molecules, mainly implicated in the retraining of the cell cycle, the repair of DNA damage, and apoptosis induced by stress responses. A result, the remaining viable cells become radio-resistant [96, 97] and will proliferate and grow in order to spread to secondary sites, subsequently resulting in organ failure. Recently, the involvement of miRNAs in promoting radiosensitivity by enhancing apoptosis has been the center of efforts [98] which suggests them as promising therapeutic targets for radioresistant tumor progression.

The family of miR-29, comprises three members, namely miR-29a, -29b, and – 29c, is capable of precipitating in the carcinogenesis and malignant transformation of various cancers [99–101]. However, the mechanism of miR-29 contribution to the elevation of radio-resistance in CC is yet not clarified. Downregulation of miR-29a is found in radioresistant CC cells (RR-CaSki cells). In fact, miR-29a could serve as a critical tumor suppressor, and it can restrict the malignant transformation process in CC cells [102]. Enforced miR-18a expression in CC cell radio-resistance including SiHa and HeLa cells, leads to re-sensitizing the CC cells to radiotherapy by enhancing apoptosis through targeting ATM, a key protein in DNA damage response. Upregulated miR-218 enhances the radiation-induced apoptosis in CC cells [102]. Furthermore, miR-145 is established to promote apoptosis-induced radiotherapy in CC cells. Taken together, these data suggest miRNAs as promising candidates implicated in augmenting radiosensitivity and escalating the apoptotic effect to alleviate the radio-resistance of CC cells.

Outnumbered research has established miR-143 as a tumor suppressor that is downregulated in many malignancies, such as CC [103–106]. Downregulation of miRNA-143 is in fact associated with tumor size and lymph node metastasis of CC [107]. Besides, miRNA-143 participates in the chemosensitivity of several malignancies and its overexpression is found to suppress CC progression and restrict migratory and invasive activity [103, 108, 109]. Recently, Esfandyari et al. [110] confirmed

that miR-143 could enhance cisplatin-induced apoptosis and the sensitivity of CaSki cells to lower doses through altering the expression of apoptosis-related genes including Bcl-2, Bax, and caspase-9 [110]. As eluded in Fig. 1, miR-143 can also stimulate CC cell apoptosis through inhibiting HIF-1α, which can protect CC cells from irradiation-induced apoptosis through downregulating p53 [111]. In this regard, Zhao et al. [112] established that ectopic expression of miR-143 could enhance CC cell apoptosis by negatively regulating HIF-1α [112]. Also, upregulation of miR-143 is found to inhibit HeLa cell proliferation and elevate apoptosis. Furthermore, Bcl-2 is targeted by miR-143 [105], resulting in elevated apoptosis rate in CC cells (SiHa and HeLa cells) [113]. Besides, upregulation of miR-143 expression is shown to reduce Bcl-2 expression while increasing Bax expression in HeLa cells following 5-Aminolevulinic acid photodynamic therapy (ALA-PDT) [114]. As well, the downregulation of miR-143 expression suppresses the influence of ALA-PDT on Bcl-2/Bax protein expression [115]. In conclusion, upregulated miR-143 mediated by the ALAPDT method results in the induction of cervical cancer cell apoptosis by negatively and positively regulating Bcl-2 and Bax levels.

Anti-apoptotic MicroRNAs in cervical cancer

Among miRNAs with the ability to regulate apoptosis, many are identified as anti-apoptotic in CC. This distinction relies on experimental results from a particular cell type. As far as we know and according to the available literature, 28 miRNAs have been shown to inhibit apoptosis, suggesting they may be onco-miRs in CC (Table 2). For example, miR-146a, -766-5p, -205-3p, -501, -378, -543, -574-5p, -141-5p, and – 15a-5p levels were found to be upregulated in CC tissues and also elevate the apoptosis of CC cell lines by directly targeting TRAF6 [116], SCAI [117], DDI2 [118], CYLD [119], ST7L [120], BRIP1 [121], QKI [122], BTG1 [123], and TP53INP1 [124], respectively. Interestingly, some miRNAs including miR-22, -425, -204, -130b-5p, -338-3p, -181, and – 543 have been found to either promote or inhibit the apoptosis of CC cell, suggesting its dual function in cancer progression, which will be briefly discussed below.

Among the THBS protein family, thrombospondin-2 (THBS2) is an extracellular matrix (ECM) protein that can regulate cell migration, apoptosis, and cytoskeleton after secretion from stromal fibroblasts, endothelial cells, and immune cells. HBS2 could suppress angiogenesis through controlling matrix metalloproteinases (MMPs) and ECM proteins [13]. MiR-1246/THBS2/ECM signaling pathways seem to be implicated in CC metastasis. Depending on the cancer type, the level of THBS2 expression varies, and in CC [125], gastric cancer [126], and ovarian cancer [127], it appears to be downregulated. At the same time, it appears to be overexpressed in pulmonary adenocarcinoma [128], and prostate cancer [129], suggesting that THBS2 could serve other protumoral functions. Therefore, a controversial role could be described for THBS2 in tumorigenesis. Recently, Zhou and colleagues [130] found that THBS2 and miR-20a expression are notably reduced and increased, respectively, in CC tissues and cells and have an inverse association with miR-20a expression in CC tissues. Moreover, inhibition of miR-20a leads to suppressed proliferation, elevated apoptosis, and mitigated autophagy in CC cells [130]. Altogether demonstrated that suppressed proliferation, autophagic activity, and promoted apoptosis are due to the downregulation of miR-20a which targets THBS2 in CC cells. These sheds light on the implication of miR-20a in CC development.

As eluded in Fig. 1, miR-1246 is able to suppress CC apoptosis through the THBS2/MMP signaling pathway. Downregulation of MMP2/9 levels and upregulation of the ECM are after miR-1246 knockdown, indicates THBS2/MMP/ECM axis as a pathway for this miRNA to regulate CC cell pathogenesis [131]. In addition, miR-181a, as one of the members of the miR-181 family, inhibits CC cell apoptosis through negatively regulating the PTEN/Akt/FOXO1 axis [132].

As can be seen in Table 2, miR-181a and – 181b are overexpressed in CC tissues. Functionally, it has also been observed that miR-181b contributes to the progression of CC via suppressing apoptosis and promoting cell proliferation through downregulating adenylyl cyclase 9 (AC9) in CC cells [133]. Overexpression of protein kinase C delta (PRKCD) can be targeted by miR-181a to stimulate the apoptosis resistance of CC in response to radiation therapy [134]. In fact, PRKCD appears to be critical to mounting an apoptotic response under stress conditions [135, 136]. Therefore, negative regulation of PRKCD by miR-181a mediates radio-resistance through enhancing cancer cell apoptosis [137]. Thus, targeting miR-181a could be a novel approach to sensitizing CC to radiation therapy. The tumor suppressor gene Phosphatase and tensin homolog (PTEN) encodes dual-specificity phosphatase [138] and comes second among frequently mutated genes in cancers after P53, thereby its inactivation is pivotal in tumorigenesis and tumor development [139]. The mechanism of PTEN for tumor suppression involves various pathways, such as FAK [140], the MAPK [141, 142], and the PI3K/AKT pathway [143, 144]. The PI3K/AKT pathway is considered the most critical one for PTEN to exerts its antioncogenic effects. As appears in Fig. 1, PTEN is able to inhibit PI3K/AKT signaling, subsequently triggering cell cycle arrest at the G1 phase and inducing apoptosis in cancer cells [145]. In fact, PTEN level in the CC tissues exhibits a downregulation in contrast to non-carcinoma tissues [117]. Moreover,

Table 2 Anti-apoptosis MicroRNA in cervical cancer cells

MicroRNA (Expression)	Target	Samples	Note	Ref
miR-454-3p	TRIM3	In vitro (SiHa and C-33 A cells)	MiR-454-3p suppresses CC cell apoptosis by targeting TRIM3.	[290]
miR-425-5p	AIFM1	In vitro (HeLa cells)	MiR-425-5p inhibits CC cell apoptosis by targeting	[291]
miR-20a (Up)	THBS2	Human (CC tissues), In vitro (SiHa and HeLa cells)	MiR-20a inhibits the apoptosis and induces the autophagy of CC cells by targeting THBS2.	[130]
miR-1246	THBS2	In vitro (SiHa cells)	MiR-1246 suppresses CC cell apoptosis by regulating THBS2/MMP signaling pathway.	[131]
miR-96-5p (Up)	SFRP4	Human (CC tissues), In vitro (SiHa and HeLa cells)	MiR-96-5p inhibits CC cells apoptosis by targeting SFRP4.	[292]
miR-27b	PLK2	In vitro (CaSki and SiHa cell)	HPV E7-upregulated miR-27b inhibits CC by targeting PLK2.	[293]
miR-130a-3p (Up)	RUNX3	Human (CC tissues), In vitro (SiHa and CaSki cells)	MiR-130a-3p inhibits cervical cancer cell apoptosis by targeting RUNX3.	[294]
miR-9	FOXO3	In vitro (SiHa cells), In vivo (mice)	MiR-9 represses CC cell apoptosis by targeting FOXO3.	[295]
miR-181a (Up)	-	In vitro (CaSKi and HeLa cells)	MiR-181a inhibits CC cell apoptosis by negatively regulating the PTEN/Akt/FOXO1 pathway.	[132]
miR-181a (Up)	PRKCD	Human (CC tissues), In vitro (Me180 and SiHa cells), In vivo (mice)	MiR-181a represses apoptosis-induced radiotherapy by targeting PRKCD in SiHa and Me180 cells.	[134]
miR-181b (Up)	AC9	Human (CC tissues), In vitro (HeLa and C-33 A cells)	MiR-181b inhibits CC cells apoptosis by negatively regulating expression level of AC9.	[133]
miR-886-5p (Up)	Bax	In vitro (SiHa cell)	MiR-886-5p inhibits the apoptosis of cervical squamous cell carcinomas by negatively regulating Bax expression levels.	[296]
miR-499a	SOX6	In vitro (SiHa cell)	Silencing miR-499a leads to the induction of cisplatin-induced apoptosis of Siha cells.	[297]
miR-22-3p	eIF4EBP3	In vitro (C33a and SiHa cells)	MiR-22-3p suppresses the apoptosis of cervical squamous carcinoma cells by targeting eIF4EBP3.	[298]
miR-155	LKB1	In vitro (HeLa cells)	MiR-155 inhibits CC cell apoptosis maybe by targeting LKB1.	[299]
miR-146a (Up)	TRAF6	Human (CC tissues), In vitro (HeLa cells)	MiR-146a represses CC cells apoptosis via inducing NF-kB signaling through targeting TRAF6.	[116]
miR-301a (Up)	PTEN	Human (CC tissues), In vitro (HeLa cells)	MiR-301a inhibits the apoptosis of CC cells by negatively regulating PTEN.	[300]
miR-1297	-	Human (CC tissues), In vitro (HeLa cell)	MiR-1297 inhibits Hela cells apoptosis maybe by targeting PTEN.	[146]
miR-766-5p (Up)	SCAI	Human (Tissues and serum samples of CC patients), In vitro (SiHa cells)	MiR-766-5p inhibits CC cell apoptosis by targeting SCAI.	[117]
miR-629	RSU1	In vitro (CaSki and SiHa cells)	MiR-629 inhibits apoptosis-induced 1′S-1′-acetoxychavicol acetate by targeting RSU1.	[301]
miR-205-3p (Up)	DDI2	Human (CC tissues), In vitro (SiHa and HeLa cells)	MiR-205-3p inhibits CC cells by targeting	[118]
miR-501 (Up)	CYLD	Human (CC tissues), In vitro (HeLa cells)	MiR-501 can inhibit CC cell apoptosis by negatively and positively regulating CYLD and NF-kB, respectively.	[119]
miR-378 (Up)	ST7L	Human (CC tissues), In vitro (SiHa and HeLa cells)	MiR-378 decreases the apoptosis of SiHa and HeLa cells by targeting ST7L.	[120]
miR-543 (Up)	BRIP1	Human (CC tissues), In vitro (SiHa and HeLa cells)	Upregulated miR-543 can inhibit SiHa and HeLa cells by targeting	[121]
miR-7-5p	STC1	In vitro (CaSki and HeLa cells)	MiR-7-5p alleviates the endoplasmic reticulum stress-mediated apoptosis in CaSki and HeLa cells maybe by targeting STC1.	[303]
miR-574-5p (Up)	QKI	Human (CC tissues), In vitro (SiHa and C-33 A cells)	Knocking down miR-574-5p leads to inducing CC cells apoptosis.	[122]
miR-141-5p (Up)	BTG1	Human (CC tissues), In vitro (HeLa and C-33 A cells)	MiR-141-5p inhibits the apoptosis of HeLa and C-33 A cells maybe by targeting BTG1.	[123]
miR-15a-5p (Up)	TP53INP1	Human (CC tissues), In vitro (SiHa and HeLa cells)	MiR-15a-5p represses CC cells apoptosis by negatively regulating TP53INP1.	[124]

PTEN expression shows an inverse association with miR-301a, and transfection of miR-301a into HeLa cells inhibits its apoptosis through reducing PTEN expression. Also, overexpression of miR-301a upregulates anti-apoptotic factors (BCL2 and MCL1), whereas it suppresses the levels of pro-apoptotic factors (BAD and BAX), thereby inhibiting CC cell apoptosis [117].

Overall, miR-301 inhibits the apoptosis of CC cells through negative regulation of PTEN. In contrast, overexpression of PTEN has been established by Chen et al. [146] which can be targeted by miR-1297 in CC cells. They observed that downregulation of PTEN represses proliferation and suppresses apoptosis in HeLa cell, similar to miR-1297 overexpression. In return, enforced miR-1297 expression suppresses Hela cell apoptosis, maybe by targeting PTEN [146]. More studies are shown in Table 2 and Fig. 1.

Critical role of MiRNAs in regulation cervical cancer cell autophagy

Autophagy is described as a regulated, pivotal catabolic mechanism of responding to extra- or intracellular stress, resulting in cell survival or even autophagic cell death. Therefore, this major processes could occur in malignant cells, and is under extreme regulation of some autophagy-related genes (ATGs) [147].

Since autophagy is essential for cell survival in harsh situations, and the degradation of intracellular macromolecules (which leads to providing energy for minimal cell functioning in a lack of nutrients), it is challenging to determine the contribution of autophagy to cell survival or death in terms of cancer regulation. Autophagy can be protective in the early stages of cancer progression or act as a tumor suppressor through triggering pro-autophagic genes and suppressing anti-autophagic ones [147, 148]. However, through regulating various cascades such as Beclin-1, Bcl-2, PI3K, mTORC1/C2 and p53, autophagy can serve as a pro-tumor role in carcinogenesis [149]. In fact, miRNAs are found as critical regulators in the autophagy process [150, 151]. Furthermore, deregulation of autophagy-related miRNAs appears to be correlated with various diseases, such as different types of cancer [152]. Several studies have reported that miRNAs affect CC progression by regulating autophagy. Among them, according to published results, we found that three miRNAs induce autophagy in CC cells (Table 3). In that regard, Wang et al. [153] established that the miR155-5p expression contrasted with the function of autophagic marker proteins (P62 and LC3) in CC tissues. In addition, transfection of miR-155-5p into CC cell lines enhanced autophagy. Furthermore, in contrast to HPV – human cervical tissues, HPV + samples exhibit a downregulated level of miR-155-5p expression and decreased autophagy [153, 154]. Considering the close association of high risk HPV infections with the occurrence of CC [50], HPV infection could result in a suppressed level of miR-155-5p which leads to decreased autophagy [153]. As eluded in Fig. 2 through targeting PDK1, miR-155-5p aggravates CC cells autophagy. In fact, PDK1 serves as a critical junction point for several cell signaling cascades and is always hyperactivated in human cancers. Therefore, PDK1 appears to be a promising target in cancer therapy. PDK1 elevates the activity of mTOR by regulating the PI3K/Akt cascade, thereby suppressing autophagy. PDK1 suppresses cellular autophagy by elevating mTOR activity [155–157]. MiR155-5p promotes cell autophagy by suppressing PDK1 and thus suppressing mTOR activity [158]. Wang et al. [153] demonstrated that transfection of mir-155-5p in CC cells elevates autophagy activity while decreasing the expression of PDK1. The effect was reversed after transfection with miR-155-5p inhibitor [153]. Therefore, miR-155-5p increases the CC cell's autophagy by targeting PDK1. As mentioned above, miR-20a acts as an onco-miRNA and elevates CC progression through apoptosis inhibition and autophagy induction through targeting THBS2. Reduction of miR-20a has shown to reduce proliferation and autophagy while inducing apoptosis by targeting THBS2 in CC cells. In contrast, miR-197 is able to inhibit autophagy by targeting Ring Finger Protein 113 (RNF113A) which can result in suppression of CC progression [159]. In return, miR-204 and − 338 alleviate CC development through suppressing autophagy and elevating apoptosis by targeting Activating transcription factor 2 (ATF-2) [160, 161]. Considering the dual role of autophagy in tumor promotion and suppression, miRNAs can regulate tumorigenesis by both inhibiting and inducing autophagy pathways. So, more studies are needed in this field.

Several autophagy-related proteins are identified to regulate multiple stages of the autophagy formation. Since their discovery in 1991 [162, 163], more than 40 genes have been identified in yeast that encode Atg proteins [164]. Most of the genes (e.g. Atg1-10, Atg12-14, Atg16-18) are conserved among mammals and yeast, suggesting the evolutionary conservation of the autophagy process [165]. In between, ATG4B is critical for the formation of autophagosomes, thereby appear to be important in cancer treatment through regulating autophagy [166]. Generation of MAP1LC3-I through proteolytic cleavage of cytoplasmic MAP1LC3/LC3 (microtubule- associated protein 1 light chain 3) is a critical step in autophagosome formation, which results in creating membrane-bound MAP1LC3-II [167]. The cysteine protease ATG4B and its paralogs catalyze this essential step, and are also required to recycle MAP1LC3 from the autophagosomal membrane [167, 168]. In that context, targeting ATG4B is established to enhance the chemotherapeutic effect in various cancer cells [169–171]. In that regard,

Table 3 MicroRNA-regulated autophagy in cervical cancer cells

MicroRNA (Expression)	Target	Samples	Function in cervical cell autophagy	Note	Ref
miR-197	RNF113A	Human (Cervical squamous cell carcinoma tissues), In vitro (CESC cells)	Promotes	MiR-197 inhibits proliferation and enhances autophagy of cervical squamous cell carcinoma by targeting RNF113A.	[159]
miR-155-5p	PDK1	In vitro (C33A, Siha and HeLa cells)	Promotes	MiR-155-5p aggravates CC cells autophagy by targeting PDK1.	[153]
miR-20a	THBS2	In vitro (SiHa and HeLa cells)	Promotes	Silencing miR-20a leads to the autophagy suppression in CC cells by targeting THBS2.	[130]
miR-21	PTEN	In vitro (SiHa cells)	Inhibits	MiR-21 inhibits the autophagy and apoptosis of CC cells by targeting PTEN.	[235]
miR-21	PTEN	In vitro (SiHa and HeLa cells)	Inhibits	Upregulated miR-21 mediate with HIF-1α aggravates radio-resistance in CC cells by inhibiting autophagy through targeting PTEN.	[303]
miR-19-3p (Up)	PTEN	Human (CC tissues), In vitro (SiHa and HeLa cells)	Inhibits	MiR-19-3p inhibits autophagy and apoptosis of CC cells by targeting PTEN.	[236]
miR-9-5p (Up)	SOCS5	Human (CC tissues), In vitro (SiHa cells)	Inhibits	MiR-9-5p alleviates CC autophagy by decreasing autophagosome through targeting SOCS5.	[304]
miR-204	ATF2	In vitro (C33A cells)	Inhibits	MiR-204 inhibits autophagy and incudes apoptosis of CC cells by targeting ATF2.	[160]
miR-338 (Down)	ATF2	Human (CC tissues), In vitro (SiHa and HeLa cells)	Inhibits	MiR-338 alleviates CC cells autophagy by activating mTOR pathway through negatively regulating ATF2.	[161]
miR-30a	-	In vitro (HeLa cells)	Inhibits	MiR-30a decreases the autophagy of CC cells induced with Hydroxycamptothecin (HCPT).	[305]
miR-34-5p	ATG4B	In vitro (SiHa and HeLa cells)	Inhibits	MiR-34-5p induces sensitivity of CC cells to pirarubicin by suppressing pirarubicin-induced autophagy through targeting ATG4B.	[175]
miR-875-5p	MDM4	In vitro (CC cells)	Inhibits	Silencing miR-875-5p leads to induction of the CC cells autophagy by targeting MDM4.	[306]
miR-224-3p	FIP200	In vitro (HPV-16$^+$SiHa, and HPV-18$^+$Hela)	Inhibits	MiR-224-3p suppresses CC cells autophagy by negatively regulating FIP200.	[307]
miR-378	ATG12	In vitro (HPV-16$^+$SiHa, and HPV-18$^+$Hela)	Inhibits	MiR-378 inhibits the autophagy of CC cells by targeting ATG12.	[176]
miR-106a	LKB1	In virto (HPV-positive SiHa and HeLa cells)	Inhibits	MiR-106a alleviates the CC cells autophagy by targeting LKB1.	[308]

pirarubicin (THP) [172], has been introduced as an effective strategy against various tumors while exposing minimum side effects [172–174]. However, most CC patients exhibit no sensitivity to THP treatment, which occurs through unknown mechanisms are not clear. Wu et al. [175] confirmed the resistance of CC cells to THP both in vitro and in vivo. In addition, they suggested that THP could induce a macroautophagy/autophagy response in CC cells, and inhibition of this autophagy elevated the cytotoxicity of THP. Moreover, THP elevated the mRNA level of ATG4B in CC cells by enhancing mRNA stability without affecting its transcription. As expected, miRNA regulation is involved in the process, as THP downregulates miR-34c-5p levels which is associated with elevated levels of ATG4B and autophagy (Fig. 2). Upregulation of miR-34c-5p significantly suppresses the level of ATG4B and attenuated autophagy, along with elevated cell death and apoptosis in THP-treated CC cells. Altogether, miR-34-5p promotes CC cell's sensitivity to pirarubicin through inhibiting pirarubicin-induced autophagy by targeting ATG4B [175]. This provides new insight for elevating the chemotherapeutic effect of THP and further clinical THP therapy for CC.

Moreover, ATG12, among ATG family members that are associated with autophagy could be targeted and subsequently decreased by miR-378 in CC cells. Suggesting miR-378 as an oncogene to promote metastasis and inhibit autophagy through targeting ATG12 in CC [176].

Recently, Tan et al. [176] observed an upregulation in the level of miR-378 and a downregulation in the ATG12 level in CC tissues with lymph node metastasis in contrast to lymph node-negative subjects [176].

As aforementioned, autophagy prevents tumor formation. It has been established that loss of BECLIN 1, the master autophagic gene, results in elevated susceptibility to tumor development [177]. Moreover, autophagy contributes to tumor metabolism and growth during Ras-induced transformation and tumorigenesis [178]. It has been suggested that tumor suppressors modulate autophagy [177]. For instance, AMPK and PTEN induce autophagy, as well, oncogenes that activate mTOR, block autophagy [179]. Recently, Wang et al. [180] established

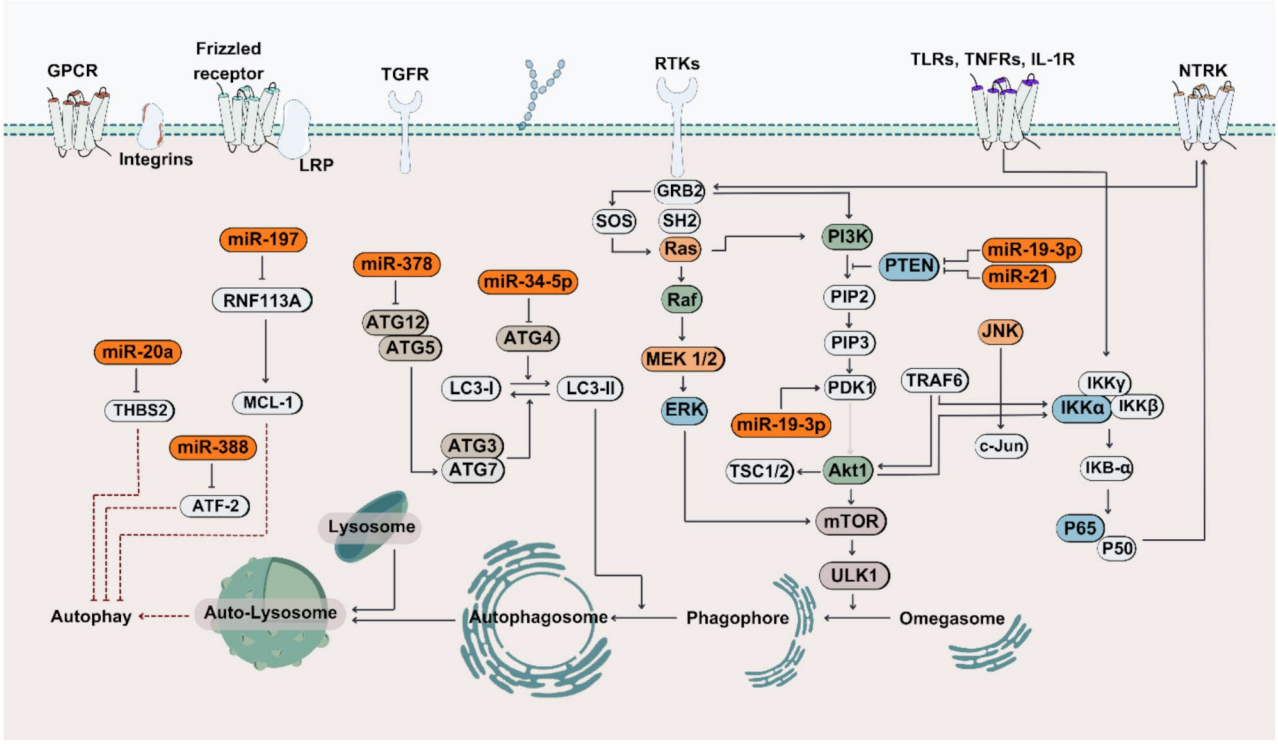

Fig. 2 Cancer cell autophagy and regulatory non-coding RNAs. Regulatory microRNAs are highlighted in orange

that the relative expression of PTEN mRNA in CC tissue samples is significantly lower than in the normal samples. Also, PTEN mRNA and protein levels in the SiHa and HeLa cells are significantly lower than those in the normal cells [180]. Besides, a negative correlation has been established between the levels of miR-19-3p with PTEN in CC cells. In fact, miR-19-3p is found to be able to target 3′-UTR of PTEN in SiHa and HeLa cells. Furthermore, their data confirmed that ectopic expression of miR-19-3p accelerates CC cell proliferation but suppresses autophagy and apoptosis through targeting PTEN [180]. Similarly, Peralta-Zaragoza et al. demonstrated an inverse association between miR-21 expression and PTEN mRNA level in SiHa cells along with PTEN protein expression in CC cells. Besides, they found that miR-21 negatively regulates the PTEN gene in CC cells by interacting with the MRE21 recognition sites of the PTEN gene. Moreover, miR-21 silencing promotes autophagy and apoptosis of CC cells and reestablishes PTEN gene and protein expression. Overall, miR-21 promotes cervical cancer development by inhibiting autophagy and apoptosis through negatively regulating PTEN. It should be noted that autophagy could contribute to the development of radio-resistance [181]. It might elevate or suppress radio-resistance, depend on the cancer types and tumor microenvironment [181]. Song et al. [182] established that overexpression of miR-21 in radioresistant CC is related to upregulated HIF-1α. In addition, upregulated miR-21 suppresses PTEN, elevates p-Akt, and consequently elevates HIF-1α expression, whereas miR-21 suppression leads to enhanced PTEN, diminished p-Akt, and eventually diminished HIF-1α (Fig. 2). In that regard, through the PTEN/Akt/HIF-1α pathway, miR-21 suppresses autophagy, which is among potential mechanisms of increasing radio-resistance in CC cells [182]. Overall, upregulated miR-21 mediate with HIF-1α aggravates radio-resistance in CC cells by inhibiting autophagy through targeting PTEN. These data expand our knowledge on controlling radio-resistance development in CC by regulating autophagy through microRNAs.

MicroRNAs effect on the ferroptosis, pyroptosis and anoikis in cervical cancer

Ferroptosis

Iron-dependent cell death, termed Ferroptosis, is a unique pathway discovered after exposure of tumor cells to erastin, a small-molecule chemical probe. There are several morphological characteristics for distinguishing ferroptosis from other modes of death, including fractured MOM, reduced mitochondrial volume, a diminished or lack of mitochondrial crest, and a normal-sized nucleus without nuclear concentration [183]. In normal conditions the oxidization of polyunsaturated fatty acids (PUFAs) is due to the function of lipoxygenases such as 12-/15-lipoxygenases. However, a rapid reduction in the levels of lipoxygenase-oxidized PUFAs occurs

as a result of the lipid repair enzyme glutathione peroxidase 4 (GPX4) function and its cofactor glutathione (GSH) [184]. Inhibition of the cystine–glutamate antiporter (system Xc–, encompassing subunits SLC3A2 and SLC7A11) induces ferroptosis and results in suppressed GSH biosynthesis and inactivation of GPX4 [185]. Therefore, overwhelming lipid peroxidation leads to subsequent cell death (Fig. 3) [186].

System XC – inhibitors, including sorafenib and sulfasalazine are compartmentalized as class I ferroptosis-inducing substances [187]. RSL3, which is able to rapidly induce ferroptotic cell death by covalent binding and blocking GPX4, represents class II ferroptosis-inducing substances [185]. The ferroptosis suppressor protein 1 (FSP1) is a flavoprotein that contributes to induction of apoptosis. Initially synthesized in mitochondria, CoQ10 has an essential role in the mitochondrial electron transport chain, and its reduced form, CoQ10H2 is a strong lipophilic antioxidant [188]. FSP1 recruitment to the plasma membrane leads to the exertion of an oxidoreductase function, reducing CoQ10. Subsequently, CoQ10H2 strongly ceased the lipid peroxides dissemination [189]. Since ferroptosis can occur in response to the peroxidation of membrane phospholipids possessing PUFAs [187], enzymes involved in the incorporation of PUFAs into phospholipids are essential for ferroptotic cell death. One example of such a critical enzyme for the execution of ferroptosis is acyl-CoA synthetase long-chain family member 4 (ACSL4) which results in the enrichment of long PUFAs in cell membranes. The autophagy machinery components, including BECN1, ATG3, ATG4B, ATG5, ATG7, and ATG13, can also trigger ferroptosis [37, 190].

Furthermore, the reduction of erastin's effects on ferroptosis due to diminished levels of intracellular ferrous iron is led by knockout or knockdown of the major genes regulating autophagy [191]. Additionally, ferritinophagy, a proteolytic process that mediates the delivery of ferritin to autophagosomes and engenders reactive oxygen species (ROS), eventually leads to ferroptosis [192, 193]. Noteworthy, miRNA is established to regulate

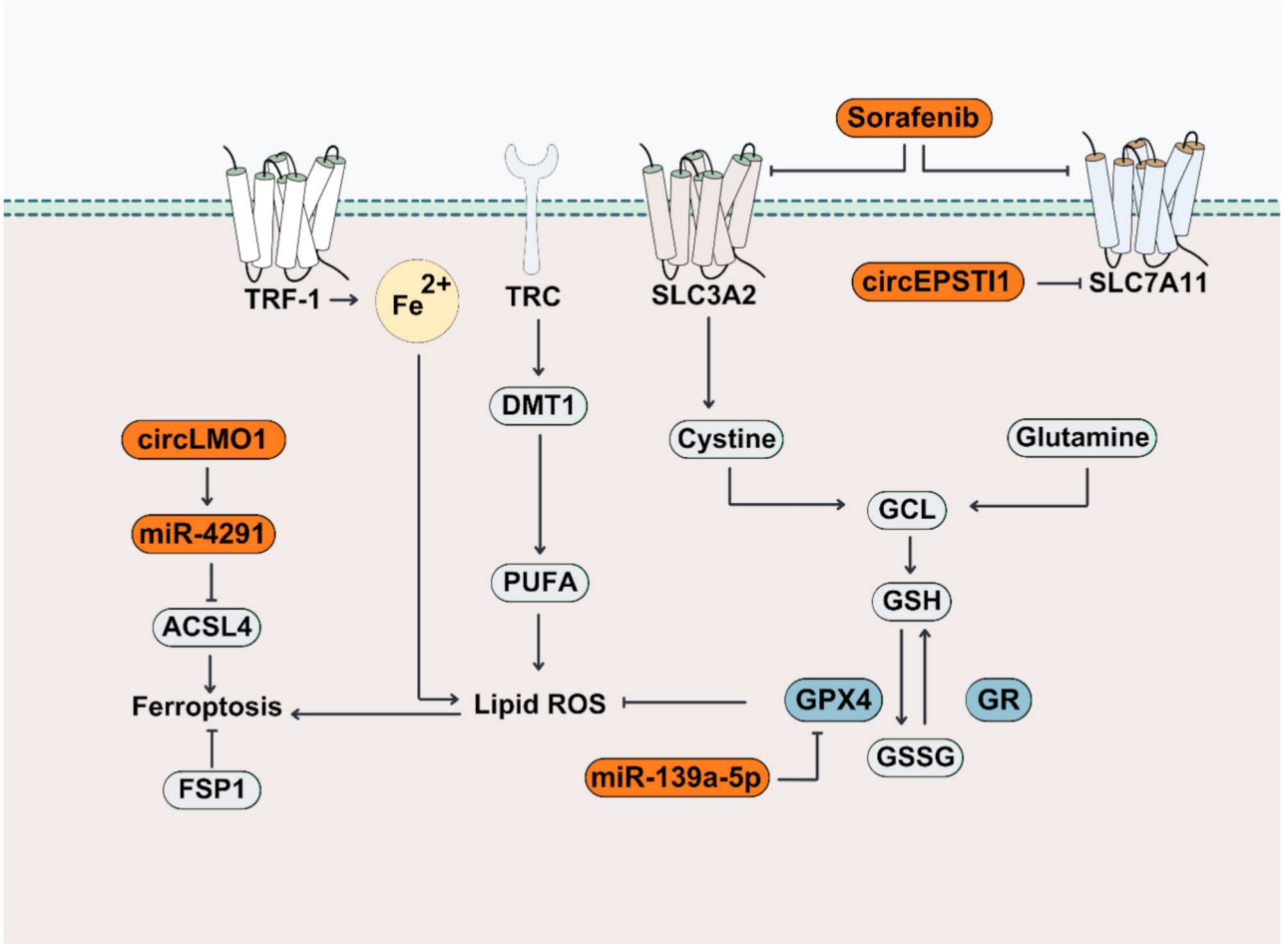

Fig. 3 Ferroptosis in cancer cells and regulatory non-coding RNAs. Regulatory microRNAs are highlighted in orange

ferroptosis by targeting mRNAs associated with ferroptosis [194–196].

Ferroptosis-associated miRNA pose several during tumor metastasis, for instance, in regulation of tumor cells, immune cells, and angiogenesis [195, 197]. For example, miR-506-3p elevates CC cell ferroptosis by targeting CD164 and by promoting the level of MDA, lipid ROS, and iron [198]. Furthermore, miR-515-5p, -409-3P and – 375 promote ferroptosis in HeLa cells by targeting SLC7A11 [199].

Glutathione peroxidase 4 (GPX4) is the core regulator of ferroptosis [200] which is highly regulated at many levels through its expression and synthesis. Targeting GPX4 hold a promise in inducing ferroptosis and eliminating resistant tumors. In that regard, many pharmacological therapeutics are developed to activate ferroptosis through targeting GPX4 in cancer cells [200]. In this regard, Liu et al. [201] suggested that miR-193a-5p can decrease CC cell viability by promoting ferroptosis by targeting GPX4. Besides, they found that circACAP2 enhances CC cell proliferation and viability by positively regulating GPX4 expression levels through sponging miR-193a-5p. The expression of circACAP2 and GPX4 is elevated, and miR-193a-5p expression is decreased in clinical CC samples. The expression of miR-193a-5p exhibits a negative association with circACAP2 and GPX4, whereas the circACAP2 expression has a positive association with GPX4. Also, suppression of miR-193a-5p or upregulation of GPX4 inhibits the circACAP2 depletion-induced lipid ROS, iron, and Fe2 + levels in CC cells [201]. Therefore, miR-193a-5p promotes ferroptosis by targeting GPX4 and serves as tumor suppressor in CC cells (Fig. 3).

Mounting evidence suggested a high occurrence rate for ferroptosis in cancer cells [202]. Sorafenib is an agonist of ferroptosis and is used as the first-line of treatment for advanced hepatocellular carcinoma (HCC). In that regard, in HCC cells, deferoxamine is shown to diminish the toxic effect of sorafenib [203]. ACSLs, a family of enzymes that mediate fatty acid metabolism, are implicated in promoting ferroptosis through producing lipid peroxides, thereby are considered as ferroptosis biomarkers [204]. Xiaofei et al. [205] established that oeanolic acid suppress the proliferation of CC cells by influencing ACSL4-dependent ferroptosis [205]. Additionally, upregulated circular RNA circEPSTI1 elevates CC growth through negative regulation of SLC7A11-dependent ferroptosis [206]. MiR-4291 as onco-miRNA contributes to CC development by inhibiting ferroptosis. Mechanically, miR-4291 suppresses ferroptosis in C33A and CaSki cells through negative regulation of ACSL4 expression. In return, circLMO1 downregulates CC growth and metastasis by promoting ferroptosis through sponging miR-4291 and positively regulating ACSL4 levels [207].

Pyroptosis

Pyroptosis, a more recently discovered PCD, is under the regulation of inflammatory caspases that coordinate biological effects [208, 209]. Various factors trigger pyroptosis cell removal. For instance, activated inflammatory caspase trigger the removal of cells [210], plasma membrane pores developed by the activated inflammatory caspase, result in swelling of cells resultant of water uptake and consequent cell lysis which occurs through disrupting the plasma membrane. Also, the disruption of membrane and leakage of cytosolic components (e.g., interleukin (IL)-1β and – 18) to the extracellular environment, amplifies the local or systemic inflammatory influences [211, 212]. Various molecular mechanisms and signaling cascades are implicated in the regulation of pyroptosis, yet, little is known about the miRNA's participations to this process. However, as far as we know, the role of only miR-214 and miR-124 in the regulation of pyroptosis in CC cells has been investigated (Table 4). Yu et al. [213] reported that in CC individuals, miR-214 and NLRP3 are downregulated. Also, the level of pyroptosis-related genes expression, such as NLRP1/3, NLRC4, caspase-1, IL-18, and – 1β are suppressed in the CC tissues. Their results established that enforcing the expression of miR-214 in Hela cells leads to inducing pyroptosis and suppresses the proliferation of CC cells by enhancing the expression of NLRP3 [213]. Similarly, miR-124 alleviates the CC pyroptosis by targeting SIRT1 (Fig. 4) [214]. According to the regulatory role of miRNAs in CC cells may mediate pyroptosis and may provide potential targets against the progression of cervical cancer. However, very limited studies have been focused on the role of miRNAs in the regulation of pyroptosis in CC, and require more attention from researchers in the future.

Anoikis

The interruption of cell–cell attachment or cell-ECM attachment results in the formation of apoptotic cell death, known as "anoikis" [215]. Anoikis has been described as a mechanism for eliminating misplaced or detached cells under physiological or pathological circumstances, which eases tissue homeostasis [216, 217]. In tumor cells, anoikis retards cell metastasis, and in addition, anoikis could occur in diabetes and cardiovascular disorders [216]. Similar to apoptosis, the initiation of anoikis occurs by the activation of the intrinsic and extrinsic pathways [42, 215]. Anoikis resistance takes place if the detached cells circumvent death signaling cascades, which enables the survival of cells as a consequence of various changes within the cell. Bcl-2 is considered a marker of the anoikis intrinsic cascade [218]. Furthermore, anoikis resistance could facilitate metastasis through promoting EMT [215]. Anoikis resistant cells exhibits malignant behaviors, such as rapid proliferation,

Table 4 MicroRNAs in regulating ferroptosis, pyroptosis, and anoikis in cervical cancer cells

MicroRNA (Expression)	Target	Samples	Function in cervical cell	Note	Ref
Ferroptosis					
miR-4291	ACSL4	In vitro (C33A and CaSki cells)	Inhibits	miR-4291 promotes cervical cancer development by inhibiting ferroptosis by targeting ACSL4.	[207]
miR-506-3p	CD164	In vitro (C33A and Hela cells)	Promotes	miR-506-3p promotes cervical cancer cell ferroptosis by targeting CD164 and by increasing the level of MDA, lipid ROS, and iron.	[198]
miR-193a-5p (Down)	GPX4	Human (Cervical cancer tissues), In vitro (HeLa and SiHa cells)	Promotes	miR-193a-5p enhances cervical cancer cell ferroptosis by targeting GPX4.	[201]
miR-515-5p, miR-409-3P and miR-375	SLC7A11	In vitro (HeLa cells)	Promotes	miR-515-5p, miR-409-3P and miR-375 maybe promote cervical cancer cell ferroptosis by targeting SLC7A11.	[199]
Pyroptosis					
miR-214	-	In vitro (Hela, SiHa, and HCC94 cells)	Promotes	miR-214 induces the pyroptosis of cervical cancer cells by regulating NLRP3 expression levels.	[213]
miR-124	SIRT1	In vitro (HeLa cells)	Inhibits	miR-124 alleviates the cervical cancer pyroptosis by targeting SIRT1.	[214]
Anoikis					
miR-525-5p (Down)	UBE2C	In vitro (HeLa cells)	Inhibition	miR-525-5p enhances the anoikis of cervical cancer cells maybe via negatively regulating UBE2C levels.	[221]

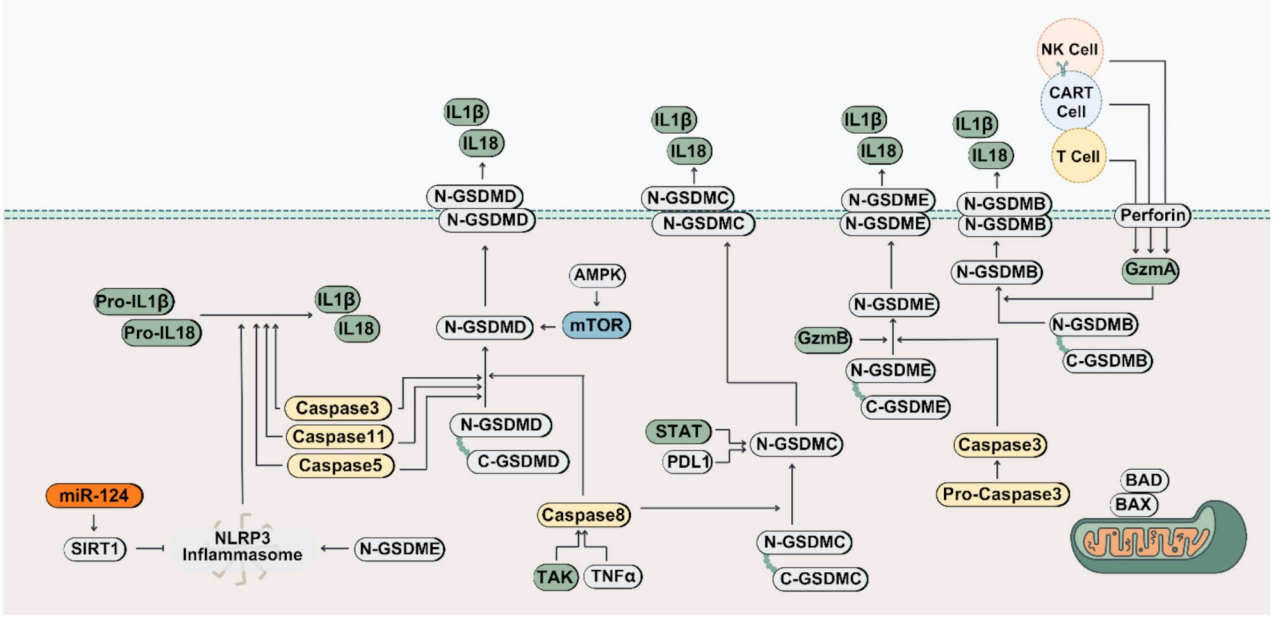

Fig. 4 Pyroptosis pathway in cancer cells and regulatory microRNAs. Regulatory microRNAs are highlighted in orange

enhanced anti-apoptotic protein levels, and an EMT phenotype. Growing evidence has established that several miRNAs expose aberrant expression levels and control metastasis-related processes, including invasion, EMT or anoikis [218–220]. High expression of miR-525-5p, an identified tumor suppressor in many malignant tumors, prevents anoikis resistance and growth independent of anchorage in CC cells. Higher expression of miR-525-5p has been demonstrated to elevate Bax expression, the predominant pro-apoptotic protein in anoikis, and suppress Bcl-2 expression, which is the major anti-apoptotic protein in anoikis [221]. Ubiquitin-conjugating enzyme E2C (UBE2C), a potential oncogene, is implicated in tumorigenesis or tumor progression [222]. Upregulation of UBE2C has been established in CC individuals and cell lines [223, 224]. In addition, UBE2C contributes to cancer progression, invasion, and metastasis through inducing EMT and regulating of angiogenic responses [223]. ZEB1/2 (zinc fnger E-box binding homeobox 1/2) are transcription factors that are aberrantly expressed in CC [225]. In fact, ZEB1/2 are identified to elevate invasion and EMT in CC cells and are upregulated after they are

directly targeted by UBE2C [226–229]. Recently, Chen et al. [230] demonstrated that UBE2C itself is directly targeted by miR-525-5p, suggesting that miR-525-5p can downregulate the levels of ZEB1/2 expression. Therefore, miR-525-5p/UBE2C/ ZEB1/2 pathway is found to mediate CC progression. Besides, they found that miR-525-5p suppressed adhesion to trigger the EMT but elevated anoikis to inhibit metastasis through interrupting UBE2C/ZEB1/2 signaling cascade [230]. Therefore, this data established the roles of miR-525-5p in CC metastases, which contributed to anoikis resistance and anchorage-independent growth, thereby suggesting miR-525-5p as a target for CC treatment.

Conclusion and future perspective

The promotion of cell death through microRNAs (miRNAs) presents a promising avenue for the development of anticancer therapies, particularly for solid tumors such as cervical cancer. Two primary strategies can be employed to harness the potential of miRNAs in this context: the first involves the therapeutic replacement of miRNAs that induce apoptosis in cancer cells, while the second focuses on the selective silencing of anti-programmed cell death (anti-PCD) miRNAs. The reduction of anti-PCD miRNAs is crucial, as these molecules inhibit programmed cell death, thereby facilitating cancer cell survival and contributing to resistance against chemotherapeutic agents [231, 232].

To effectively suppress miRNA activity, the use of miRNA inhibitors and oligomers is a viable approach. Additionally, modified miRNA mimetics, such as plasmid or lentiviral vectors that express specific miRNA sequences, may enhance the function of miRNAs that promote cancer cell death. While restoring normal miRNA expression holds significant therapeutic promise, challenges remain due to the incomplete understanding of miRNA regulation and function during their biogenesis and in the context of tumorigenesis.

To mitigate potential adverse effects associated with miRNA therapies, it is essential to investigate the immunogenic and cytotoxic impacts of in vivo miRNA delivery. Furthermore, the role of miRNAs within the complex transcription factor-like gene regulatory networks complicates the feasibility of knocking down miRNAs using anti-miRNA oligonucleotides. Current limitations in the delivery and distribution systems for miRNAs pose additional challenges to their therapeutic application. Biological vectors, such as adeno-associated viruses and lentiviruses, can facilitate targeted delivery; however, it is imperative to avoid unintended off-target effects [233].

The dual role of many miRNAs as either tumor suppressors or oncogenes, depending on the cellular context, etiology, and cancer stage, underscores the complexity of miRNA networks in tumorigenesis [234]. The intricate interplay of miRNA species derived from the 5p and 3p arms of pre-miRNA precursors further complicates their functional roles. Emerging evidence suggests that some miRNAs can regulate multiple forms of programmed cell death, making them attractive targets for overcoming resistance to cell death and enhancing sensitivity to chemotherapy in cervical cancer cells [133, 134].

The ability of miRNAs to modulate oncogenes and tumor suppressor genes positions them as potential biomarkers for early diagnosis and prognosis, as well as therapeutic targets. As we look towards the future, the implications of miRNA research could be profound, particularly in the context of personalized medicine. Advances in miRNA profiling may enable the development of tailored therapies that enhance treatment efficacy while minimizing side effects. The anticipated 2024 Nobel Prize in Medicine may further spotlight the significance of miRNAs, potentially recognizing groundbreaking discoveries that elucidate their mechanisms in cancer biology. Such recognition could catalyze increased funding and interest in miRNA-based therapies, ultimately leading to innovative treatment strategies for solid tumors like cervical cancer. However, the mechanisms underlying miRNA action remain incompletely understood, necessitating further basic research and clinical trials to validate their therapeutic applicability. As translational research progresses, a deeper understanding of miRNA dynamics and their interactions within cellular networks will be essential for developing effective therapies for solid tumors like cervical cancer [235, 236].

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