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The potential roles and mechanisms of non-coding RNAs in cancer anoikis resistance

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Abstract

Increasing evidence indicates that anoikis resistance is a critical process for metastasis of cancer cells, making it the attractive therapeutic target for cancer benefit. Anoikis resistance is widely regulated by various factors, such as signaling pathways, integrins switch, and non-coding RNAs (ncRNAs). ncRNAs composed of microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), are frequently dysregulated in a variety of human malignancies and are closely related to anoikis resistance of cancer cells. Based on the available literature, we reviewed the molecular basis underlying ncRNAs modulating cancer cells anoikis resistance, which may contribute to a better understanding of cancer metastasis and provide new beneficial therapeutic strategies against cancer.

Keywords Anoikis resistance · Non-coding RNA · microRNA · Long non-coding RNA · Circular RNA · Cancer

Introduction

Anoikis resistance is a crucial cellular program that enables carcinoma cells to escape apoptosis in the absence of attachment to extracellular matrix (ECM) or upon cell adhesion to an inappropriate location [1–3]. The ability to resist apoptosis under the loss of ECM attachment endows cancer cells to detach from the primary tumor site, invade a distant site and establish a metastatic lesion [3, 4]. Therefore, it has been believed that anoikis resistance is a critical process for tumor cell metastasis [5], and overcoming anoikis resistance may have important therapeutic value for cancers [3, 6].

Previous studies have shown that cancer cells can achieve anoikis resistance through multiple factors or mechanisms including integrins switch, growth proteins, oxidative stress, autophagy, epithelial-mesenchymal transition (EMT), metabolism, and signaling pathway [3, 5, 7]. For instance, the interplay between integrin-α2β1/-α5β1 and EGFR enhanced anoikis resistance in colon cancer cells through activating downstream effectors ERK and AKT and suppressing Caspase-3 activation [8]. Upregulation of LC3B induced by oxidative stress attenuated anoikis resistance in contrast to regulating autophagy in ovarian cancer cells [9]. Moreover, CPT1A-mediated fatty acid oxidation activation led to colorectal cancer cells resisting anoikis and increase metastatic capacity [10]. These studies suggest that anoikis resistance in cancer cells is far more complicated than expected and warrants further investigation.

Non-coding RNAs (ncRNAs), such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), are a group of RNA transcripts that do not own the protein-coding ability but are involved in the regulation of physiological and pathological functions [11–13]. Ample evidence indicated that ncRNAs have been identified as oncogenic drivers or tumor suppressors in various malignancies [14]. Notably, multiple ncRNAs are associated with anoikis resistance in various cancers [1].

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Considering the rapid development of the ncRNA field, a more detailed understanding of the molecular mechanisms underlying ncRNAs modulating cancer cells anoikis resistance is urgently needed. In this review, we focused on the critical roles of ncRNAs in modulating anoikis resistance in cancers.

Discussion

MiRNAs and anoikis resistance

MiRNAs are a kind of ~ 22-nucleotide, evolutionarily conserved ncRNAs, which modulate target gene expression through binding to the 3'-untranslated region (3'-UTR) of target mRNA molecules at the posttranscriptional level [15, 16]. Amounting evidence has shown that miRNA is involved in various processes, such as cell growth, metastasis, therapy resistance, and immune escape [17–19]. Interestingly, a variety of miRNAs can be oncogenic or tumor-suppressive and have repeatedly been implicated for their roles in regulating anoikis resistance [1, 20].

MiRNAs act as positive regulators of anoikis resistance

A growing body of evidence shows that aberrant miRNAs enhanced anoikis resistance of cancer cells through the regulation of pathways, adhesion molecules, or apoptosis-associated proteins (Table 1, Fig. 1).

Emerging data have indicated that several signaling pathways are abnormally activated or inactivated in cancers, and are vital mediators and drivers in anoikis resistance [7]. The Hippo signaling, tumor-suppressive signaling, has been frequently identified to be inactivated in multiple cancers, and the inactivation of Hippo signaling exerts a pleiotropic role in the progression and metastasis of cancers [21]. A previous study showed that miR-424-5p overexpression promoted, while miR-424-5p knockdown inhibited, anoikis resistance and lung metastasis of thyroid cancer cells in vitro and in vivo by inactivating the activity of Hippo signaling via directly targeting WWC1, SAV1, and LAST2[21]. As a key node of the Hippo signaling pathway, Yes-associated protein 1 (YAP1) has been implicated to regulate anoikis. Yu et al. noted that miR-200a overexpression promoted whereas miR-200a inhibition suppressed anoikis resistance in breast cancer cells by the downregulation of YAP1, which resulted in decreased pro-apoptotic protein expression [22]. Recent research showed that enforced expression of miR-141 enhances cell proliferation, anchorage-independent capacity, anoikis resistance, tumor growth and peritoneal metastases of ovarian cancer cells through the regulation of KLF12/Sp1/survivin axis [23]. What's more, MiR-G-10, a novel miRNA identified in G-rich RNA sequence binding protein (GRSF1) complex, promote migration/invasion and anoikis resistance in vitro and lung metastasis in vivo, by upregulating PIK3R3 expression to activate the AKT/NF-κB signal pathway and suppressing TIMP3/MMP9 pathway [24]. Hida et al. used a public tumor endothelial cell microarray database and found that miR-145, increased in tumor endothelial cell, signifiacntly elevated cell adhesion and anoikis resistance in human microvascular endothelial cells by enhancing the BCl-2 and Bcl-xL expresion via the ERK1/2 pathway [25].

Cell surface adhesion molecules have been implicated in the acquisition of anoikis resistance of cancer cells [26, 27]. Penna et al. found that miR-214 was involved in the modulation of survival to anoikis in melanoma [28]. Using a melanoma metastatic model, miR-214 was found to be highly expressed in metastatic (high) cells compared with parental (low) cells. Moreover, the introduction of miR-214 expression contributed to melanoma cell movement and survival to anoikis in vitro as well as extravasation from blood vessels and lung metastasis formation in vivo through targeting TFAP2C, which is a member of the AP-2 transcription factor family and involved in the activation or repression of

Table 1 MiRNAs promote anoikis resistance in cancers

miRNAs	Type of cancer	Target/axis	References
miR-145	Esophageal adenocarcinoma	–	[29]
miR-145	Esophageal adenocarcinoma	c-Myc/integrin	[30]
miR-145	Tumor endothelial cells	ERK1/2/Bcl-2/Bcl-xl	[25]
miR-424-5p	Thyroid cancer	WWC1, SAV1, LAST2	[21]
miR-200a	Breast Cancer	YAP1	[22]
miR-141	Ovarian cancer	KLF12	[23]
miR-G-10	Cervical cancer	PIK3R3/AKT/NF-κB; TIMP3/MMP9	[24]
miR-214	Melanoma	TFAP2C/miR-148b	[28, 88]
miR181a	Breast cancer	Bim	[32]
miR-21	Esophageal adenocarcinoma	PDCD4, PTEN	[33]

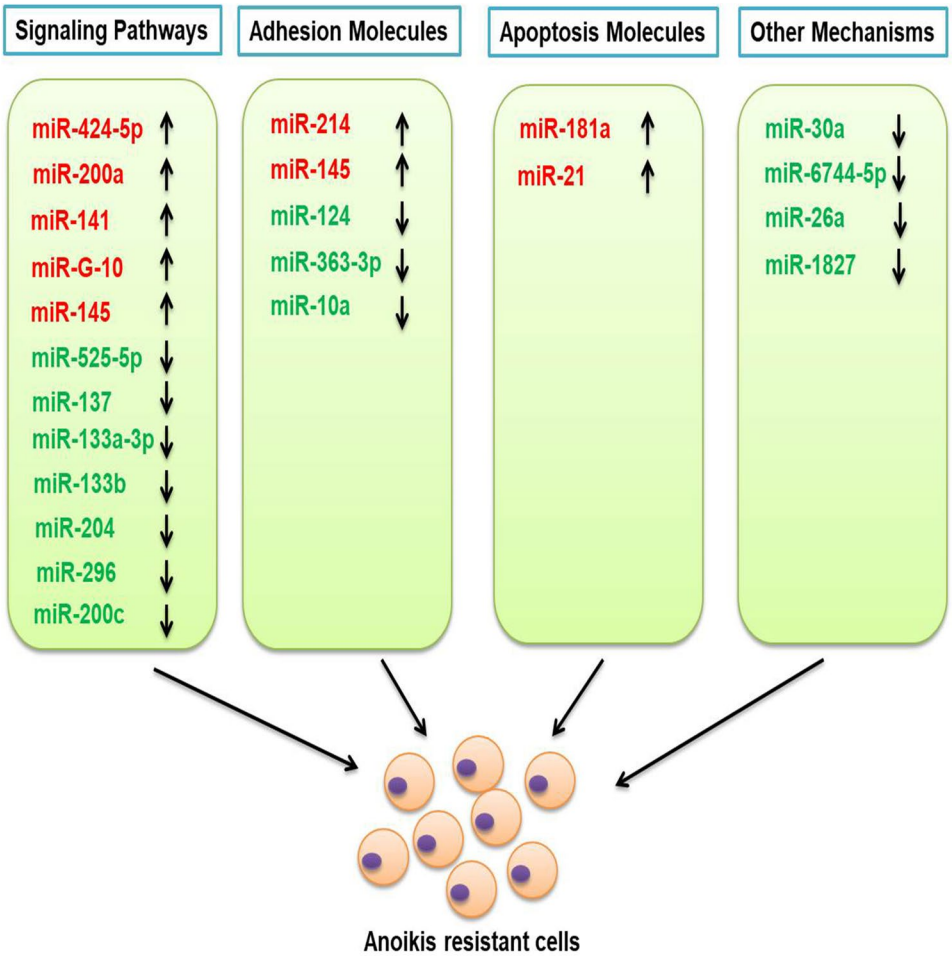

Fig. 1 microRNA (miRNA) regulates anoikis resistance in cancers via different mechanism. It is described in Tables 1 and 2

cell movement and adhesion molecules [28]. Additionally, miR-145 overexpression obviously enhanced cell invasion and anoikis resistance of esophageal adenocarcinoma cell lines (OE33, FLO-1, SK-GT-4) [29]. Moreover, upregulation of miR-145 induced resistance to anoikis and invasion potential in esophageal adenocarcinoma cells was associated with the downregulation of c-Myc, which led to the integrins subunits α5 and β3 expression [30].

Given that anoikis is a special form of apoptosis, the dysregulation of apoptosis-associated genes is observed to play a pivotal role in anoikis resistance of cancer cells [31]. Dysregulated TGF-β signaling was demonstrated to drive late-stage breast cancer metastasis. MiR-181a induced by TGF-β promoted epithelial-mesenchymal transition, migration, and invasion in breast cancer cells [32]. Mechanistically, miR-181a down-regulation significantly increased the expression of Bim, a proapoptotic protein molecule that sensitized metastatic cells to anoikis [32]. Zhao et al. hypothesized that miR-21, one of the most commonly observed aberrant miRNAs in human cancers, could contribute to tumor metastasis by regulating anoikis in human esophageal adenocarcinoma. In fact, transfection of miR-21 mimics significantly enhanced the resistance to anoikis in esophageal adenocarcinoma cells by targeting PDCD4 and PTEN, which were involved in the regulation of many basic cellular functions including cell apoptosis [33].

MiRNAs act as negative regulators of anoikis resistance

Next, we reviewed the effect of miRNAs, function as tumor suppressor gene, on anoikis resistance in cancers (Table 2, Fig. 1).

Experimental evidence reported that tumor-suppressive miRNAs also can modulate anoikis resistance of cancer cells via triggering or inhibiting signaling pathways [1, 20]. For example, the introduction of miR-525-5p, which acts as a tumor suppressor gene, dramatically hampered anchorage-independent growth and anoikis resistance of cervical cancer cells via blocking ubiquitin-conjugating enzyme E2C (UBE2C)/ZEB1/2 signal axis [34]. In pancreatic cancer, miR-137 was decreased in pancreatic cancer cells (AsPC-1 and PANC-1 cell) after the induction of anoikis in time-dependent. Overexpression of miR-137 reduced the

Table 2 MiRNAs inhibit anoikis resistance in cancers

miRNAs	Type of cancer	Target/axis	References
miR-525-5p	Cervical cancer	UBE2C	[34]
miR-137	Pancreatic cancer	PXN	[35]
miR-133a-3p	Prostate cancer	EGFR, FGFR1, IGF1R and MET; PI3K/AKT	[38]
miR-133b	Esophageal squamous cell carcinoma	EGFR	[39]
miR-204	Gastric cancer	SIRT1	[40]
miR-204	Epithelial ovarian cancer	BDNF	[41]
miR-296	Nasopharyngeal carcinoma	STAT3	[42]
miR-200c	–	FN1; MSN; LEPR; ARHGAP19	[43]
miR-200c	Ovarian cancer	TrkB	[44]
miR-200c	Triple negative breast bancer	NF-κB; TrkB/NTF3;	[45]
miR-124	Colorectal cancer	ITGA3	[48]
miR-363-3p	Papillary thyroid carcinoma	integrin alpha 6	[49]
miR-424-5p	Hepatocellular carcinoma	ICAT	[50]
miR-10a	Colorectal cancer	MMP14; ACTG1	[51]
miR-30a	Hepatocellular carcinoma	Beclin 1;Atg5	[54]
miR-6744-5p	Breast cancer	NAT1	[57]
miR-26a	Esophageal adenocarcinoma	Rb1	[58]
miR-1827	Lung adenocarcinoma	caveolin-1	[59]

resistance to anoikis in pancreatic cancer cells in vitro and in vivo by negatively modulating paxillin (PXN), which resulted in the activation of the AKT signaling pathways [35]. MiR-133a-3p and miR-133b were frequently low expression in various types of cancers and were reported to be tumor suppressors [36, 37]. In prostate cancer, upregulation of miR-133a-3p suppressed cancer stem cell-like phenotypes and attenuated anoikis resistance of prostate cancer cells by directly targeting multiple cytokine receptors, including EGFR, FGFR1, IGF1R, and MET, which further inhibited PI3K/AKT signaling [38]. Also, in esophageal squamous cell carcinoma, miR-133b negatively modulated anoikis resistance and anchorage-independent growth through the regulation of EGFR-mediated ITGB4/FAK/Grb2, AKT, and ERK signaling [39]. Zhang and collaborators verified that decreased in gastric cancer specimens, miR-204 reduced cell invasion and anoikis resistance in gastric cancer cells via modulating the SIRT1-LKB1 pathway [40]. Additionally, the miR-204 levels were significantly down-regulated in an anoikis pattern of epithelial ovarian cancer cells. Furthermore, restored expression of miR-204 enabled cells to acquire more sensitivity to anoikis through the inhibition of BDNF, contributing to the inactivation of the PI3K/AKT signaling pathway [41]. Besides, miR-296 was involved in the inhibitory effects of epigallocatechin gallate (EGCG), the most active and abundant polyphenol in green tea, on anoikis-resistant nasopharyngeal carcinoma cells through the downregulation of STAT3 activation [42]. MiR-200c, an important member of the miR-200 family that emerged as a potent regulator of epithelial to mesenchymal transition, has been implicated in the resistance to anoikis in various cancers. Howe et al. identified, using a microarray profiling, several direct targets of miR-200c, including the genes encoding fibronectin 1 (FN1), moesin (MSN), neurotrophic tyrosine receptor kinase type 2 (NTRK2 or TrkB), leptin receptor (LEPR), and Rho GTPase activating protein 19 (ARHGAP19) [43]. Among these targets, TrkB was a tyrosine kinase receptor that contributed to the ability of miR-200c to suppress anoikis resistance [43]. In ovarian cancer, restoration of miR-200c resulted in decreasing the resistance to anoikis and adherence to biologic substrates in ovarian cancer cells by targeting TrkB, a tyrosine kinase receptor [44]. Moreover, miR-200c overexpression enhanced anoikis sensitivity through the regulation of an NF-κB upregulated TrkB/NTF3 autocrine signaling loop in triple-negative breast cancer [45]. All these data indicated that miRNAs as tumor suppressor genes and regulate the cancer-associated signaling axis, leading to abnormal anoikis of tumor cells.

As transmembrane receptors, integrins are well known as adhesion molecules, which mediate cell-ECM interaction and exert important roles in regulating anoikis resistance [46, 47]. The study by Sa et al. showed that overexpression of miR-124 attenuated the anoikis resistance in colorectal cancer cells by targeting integrin alpha 3 (ITGA3), a member of integrins [48]. In addition, miR-363-3p was found to suppress anoikis resistance of papillary thyroid carcinoma cells (B-CPAP cells) by negatively modulating its target gene integrin alpha 6 (ITGA6)[49]. Moreover, decreased in hepatocellular carcinoma tissues, miR-424-5p suppressed

anoikis resistance in anchorage-independent hepatocellular carcinoma cells by targeting ICAT/CTNNBIP1, a potent b-catenin inhibitor [50]. MiR-10a, inversely correlated with distant metastasis and invasion depth of colorectal cancer, decreased cell adhesion and anoikis resistance activities by targeting matrix metalloproteinase 14 (MMP14) and actin gamma 1 (ACTG1). Furthermore, MMP14 is an ECM remodeling protein; while ACTG1 is involved in muscle contraction, cell motility, cell adhesion, and cell shape maintenance [51].

Autophagy, an evolutionarily conserved process, has been reported to be involved in the modulation of anoikis resistance in hepatocellular carcinoma [52, 53]. MiR-30a, decreased in hepatocellular carcinoma and cell lines, was proved to inhibit Beclin 1 and Atg5-dependent autophagy, and further suppress autophagy-mediated anoikis resistance and metastasis in hepatocellular carcinoma cells [54].

Reactive oxygen species (ROS) is verified to participate in the anoikis resistance [55, 56]. N-acetyltransferase 1 (NAT1), a xenobiotic-metabolizing enzyme, has been unraveled to inhibit anoikis by suppressing ROS. Moreover, NAT1-mediated inhibitory effects on anoikis resistance were abolished by miR-6744-5p in both luminal A and triple-negative breast cancer cell lines [57].

Other mechanisms including cell cycle protein engaged in anoikis resistance of cancer cells. Zhang et al. reported that the suppression of miR-26a contributed to the anoikis resistance acquisition of esophageal adenocarcinoma cells. Also, the authors found that Rb1 was the direct target of miR-26a, and revealed that the reduction of miR-26a expression leads to increased Rb1 protein level and thus inhibits the function of E2F1, by which it influences the phenotypes of cell cycle and anoikis [58]. Guo and collaborators showed that the levels of miR-1827 were decreased in non-small cell lung cancer tumor tissues and cells, and were associated with tumor grade and lymph node metastasis. The upregulation of miR-1827 suppressed anchorage-independent growth and anoikis resistance of lung adenocarcinoma A549 cells through negatively regulating the expression of caveolin-1 (CAV-1)[59], an important regulator in anoikis resistance of cancer cells [60].

Impact of lncRNAs in anoikis resistance

LncRNAs are a type of ncRNA with > 200 nucleotides in length, which had not the ability of protein-encoding [12, 61, 62]. It has been shown that lncRNAs function as important tumor modulators and participate in cancer pathogenesis, such as cell growth, metastasis, stemness, and drug resistance [63–65]. An increasing body of research has suggested that dysregulation of lncRNAs played crucial roles in the modulation of anoikis resistance in various cancers [1].

LncRNAs act as positive regulators of anoikis resistance

Accumulating evidence documents that lncRNAs can also modulate anoikis resistance of cancer cells via regulating pathways, apoptosis-associated proteins, or other molecules (Table 3, Fig. 2).

The lncRNA HOTAIR, the HOX transcript antisense intergenic RNA, is upregulated and has been associated with poor prognosis, invasiveness, and aggressiveness of various cancer types [66, 67]. Small interfering RNA (siRNA)-mediated knockdown of HOTAIR expression markedly reduced the abilities of anoikis resistance, migration, and invasion in the ovarian cancer cells under the suspension condition. Moreover, HOTAIR enhanced the anoikis resistance and spheroid forming ability of ovarian cancer cells by recruiting EZH2 and influencing H3K27 methylation [68]. In hepatocellular carcinoma, HOTAIR was also reported to be able to promote the escape from anoikis through downregulating c-Met signaling [69]. In addition, HOTAIR silencing markedly decreased the anoikis resistance of gastric cancer cells [70]. Zhang and collaborators showed that lncRNA ANRIL was positively correlated with glioma grade. Silencing

Table 3 The role of lncRNAs or circRNAs in regulating anoikis resistance in cancers

LncRNAs/CircRNAs	Type of cancer	Target/axis	References
lncRNA HOTAIR	Ovarian cancer	EZH2/H3K27	[68]
lncRNA HOTAIR	Hepatocellular carcinoma	c-Met	[69]
LncRNA ANRIL	Glioma	miR-203	[71]
LncRNA APOC1P1-3	Breast cancer	miR-188-3p/Bcl-2	[72]
LncRNA MALAT1	Ovarian cancer	RBFOX2/KIF1B	[73]
LncRNA VAL	Lung adenocarcinoma	Trim16/Vimentin	[74]
LncRNA FOXD2-AS1	Thyroid carcinoma	miR-7-5p/TERT	[75]
LINC00958	Bladder tumor	–	[76]
LncRNA-MAPK8IP1P2	Thyroid cancer	miR-146b-3p	[79]
CircSIPA1L1	Osteosarcoma	miR-411-5p/RAB9A	[85]
CircUBAP2	Lung cancer	–	[86]

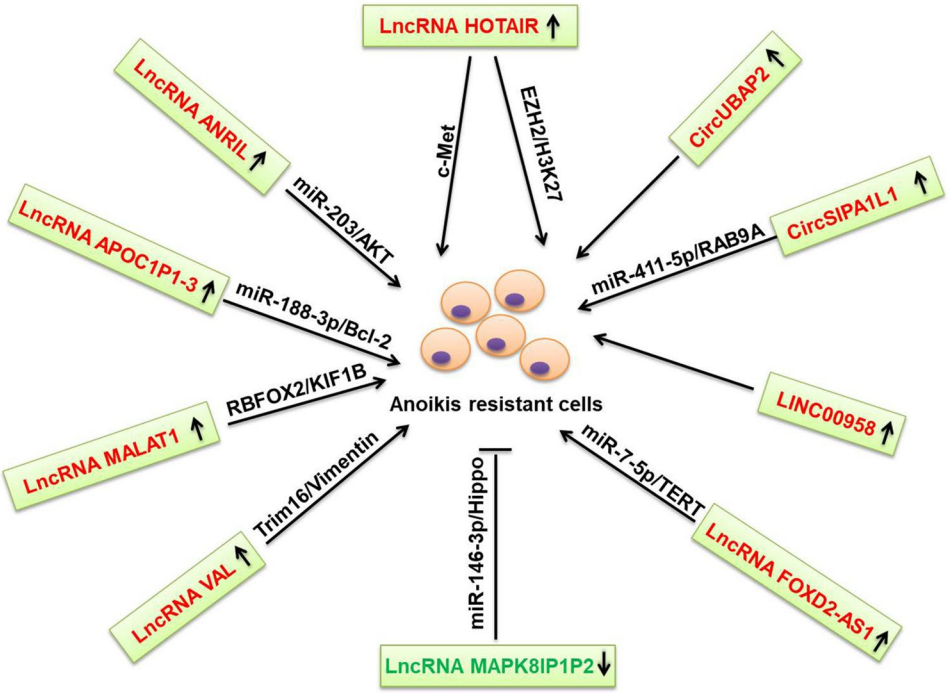

Fig. 2 Long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) regulate anoikis resistance in cancers via different mechanism. It is described in Table

lncRNA ANRIL obviously attenuated anoikis resistance and induced cell cycle arrest in G0/G1 phase, while regulating the activity of caspase-3/8/9 and the AKT signaling pathway in glioma cells. Moreover, overexpression of miR-203a could partially reverse these functions [71].

The study by Lu et al. indicated that lncRNA APOC1P1-3 was upregulated in malignant cell lines of breast cancer and was negatively associated with the survival rate of patients with breast cancer. Also, lncRNA APOC1P1-3 significantly enhanced the capacity of anoikis resistance of breast cancer cells by specifically binding to miR-188-3p to block the inhibition of Bcl-2[72]. High lncRNA MALAT1 was shown to be associated with increased stage, recurrence, and reduced survival in ovarian cancer. The expression of lncRNA MALAT1 was markedly increased in multiple anoikis-resistant ovarian cancer cell lines. Moreover, lncRNA MALAT1 suppression resulted in decreased proliferation, invasion, anchorage-independent growth, and increased anoikis by regulating RBFOX2-mediated alternative splicing of the pro-apoptotic isoform of KIF1B [73]. These data suggest that lncRNA plays a key role in anoikis resistance by affecting the expression of apoptosis-associated proteins.

Interestingly, lncRNA VAL induced by AKT signaling was found to promote cell adhesion, invasion, and anoikis resistance in lung adenocarcinoma through directly binding to Vimentin and competitively abrogating Trim16-dependent Vimentin polyubiquitination and degradation [74]. LncRNA FOXD2-AS1, upregulated in thyroid carcinoma tissues and cells, promoted cancer stem cell-like phenotypes and enhanced the anoikis resistance in vitro by sponging miR-7-5p and up-regulating the expression of telomerase reverse transcriptase (TERT) [75]. Lastly, LINC00958 was identified to be significantly upregulated in bladder tumor samples compared with normal samples. In addition, LINC00958 knockdown significantly attenuated anoikis resistance of bladder cancer cells [76].

LncRNA acts as negative regulators of anoikis resistance

As a crucial signaling pathway in cancers, inactivation of Hippo signaling is found to contributes to tumor progression and metastasis [77, 78]. LncRNA-MAPK8IP1P2, decreased in the thyroid cancer tissues with lymphatic metastasis, inhibited anoikis resistance in vitro and lymphatic metastasis of thyroid cancer cells in vivo through the activation of Hippo signaling by sponging miR-146b-3p [79].

The role of circRNAs in anoikis resistance

CircRNAs are a kind of endogenous ncRNA that are single-stranded closed-loop RNA molecules lacking terminal 5' caps and 3' poly(A) tails [80, 81]. Emerging studies showed the key roles of circRNAs in regulating tumor progression [82–84], which also are involved in the regulation of anoikis resistance (Table 3, Fig. 2). CircSIPA1L1 was highly expressed in osteosarcoma tissue samples and cell lines. Knockdown circSIPA1L1 impaired the capacities of invasion, migration, proliferation, and survival of osteosarcoma cells by regulating the RAB9A signaling pathway via

sponging miR-411-5p [85]. Yin et al. found that the expression of circUBAP2 was higher in lung cancer tissue samples than that in normal tissue samples. Moreover, circUBAP2 silencing obviously reduced the anoikis resistance of lung cancer cells [86].

Conclusions

Given that anoikis resistance is the hallmark of invasiveness, metastasis, therapy resistance, and relapse of cancer cells [7], anoikis resistance provides an attractive target for cancer therapeutic benefit. It has been reported that aberrant ncRNA expression is associated with anoikis resistance in several types of human cancers [1], suggesting that targeting ncRNA-based therapeutic strategies may obviously suppress anoikis resistance of tumor cells and further reduce the incidence of metastasis and recurrence. Anoikis resistance has been identified to be modulated by several factors including signaling pathways, cell adhesion, growth/apoptosis protein, oxidative stress, stemness, autophagy, and metabolic reprogramming [7]. Although ncRNAs exert the regulatory effects on anoikis resistance via multiple mechanisms, the role and mechanisms of ncRNA in the modulation of anoikis resistance remain to be resolved. For example, the Warburg effect, more specifically, diminished glucose oxidation, promoted anoikis resistance and metastasis in cancers [7, 87], but which and how ncRNA is involved in anoikis resistance by regulating the Warburg effect remains unclear. Hence, it is of great importance to in-depth investigate the role and mechanisms of ncRNA in anoikis resistance at the current stage. Based on our knowledge from the available literature, the role of miRNAs in anoikis resistance has been relatively demonstrated, but the effect of lncRNA and circRNA in the mechanism of anoikis resistance still largely stay in the early stage. For instance, only two circRNAs, circSIPA1L1 and circUBAP2, were verified to participate in the regulation of anoikis resistance in osteosarcoma or lung cancer [85, 86]. Therefore, further investigation is warranted to determine how specific lncRNA or circRNA influence the role of anoikis resistance in cancers. Although some problems remain for the relationship between ncRNAs and anoikis resistance, verify the detailed function and mechanism of ncRNA on anoikis resistance, which may contribute to a better understanding of cancer metastasis and provide new insights into the treatment of this disease.

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Author contributions TS, CZ, and SX performed and wrote articles, TS and CZ modified the language, TS and SX designed the articles.

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Declarations

Conflict of interest The authors declare that they have no confict of interest.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent to publication Not applicable.

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