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microRNA 21 and long non-coding RNAs interplays underlie cancer pathophysiology: A narrative review

Roberta Giordo [a], Fatemeh Abdullah M. Ahmadi [b,1], Nedal Al Husaini [b,1], Noora Rashid A.M. Al-Nuaimi [b,1], Salma M.S. Ahmad [b,1], Gianfranco Pintus [a,c,*], Hatem Zayed [b,**]

[a] Department of Biomedical Sciences, University of Sassari, Viale San Pietro 43B, 07100, Sassari, Italy
[b] Department of Biomedical Science, College of Health Sciences, Member of QU Health, Qatar University, P.O. Box 2713, Doha, Qatar
[c] Department of Medical Laboratory Sciences, College of Health Sciences and Sharjah Institute for Medical Research, University of Sharjah, University City Rd, Sharjah, 27272, United Arab Emirates

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ABSTRACT

Non-coding RNAs (ncRNAs) are a diverse group of functional RNA molecules that lack the ability to code for proteins. Despite missing this traditional role, ncRNAs have emerged as crucial regulators of various biological processes and have been implicated in the development and progression of many diseases, including cancer. MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are two prominent classes of ncRNAs that have emerged as key players in cancer pathophysiology. In particular, miR-21 has been reported to exhibit oncogenic roles in various forms of human cancer, including prostate, breast, lung, and colorectal cancer. In this context, miR-21 overexpression is closely associated with tumor proliferation, growth, invasion, angiogenesis, and chemoresistance, whereas miR-21 inactivation is linked to the regression of most tumor-related processes. Accordingly, miR-21 is a crucial modulator of various canonical oncogenic pathways such as PTEN/PI3K/Akt, Wnt/β-catenin, STAT, p53, MMP2, and MMP9. Moreover, interplays between lncRNA and miRNA further complicate the regulatory mechanisms underlying tumor development and progression. In this regard, several lncRNAs have been found to interact with miR-21 and, by functioning as competitive endogenous RNAs (ceRNAs) or miRNA sponges, can modulate cancer tumorigenesis. This work presents and discusses recent findings highlighting the roles and pathophysiological implications of the miR-21-lncRNA regulatory axis in cancer occurrence, development, and progression. The data collected indicate that specific lncRNAs, such as MEG3, CASC2, and GAS5, are strongly associated with miR-21 in various types of cancer, including gastric, cervical, lung, and glioma. Indeed, these lncRNAs are well-known tumor suppressors and are commonly downregulated in different types of tumors. Conversely, by modulating various mechanisms and oncogenic signaling pathways, their overexpression has been linked with preventing tumor formation and development. This review highlights the significance of these regulatory pathways in cancer and their potential for use in cancer therapy as diagnostic and prognostic markers.

1. Introduction

Over the last few decades, after the ground-breaking completion of the Human Genome Project (HGP), it became evident that only about 1.5 % of the human genome accounts for protein-coding sequences, while the other 98.5 % is non-coding and does not provide instructions for making proteins [1,2]. Moreover, as a result of the recent technological advancement in high-throughput sequencing, large data sets were quickly and efficiently generated and analyzed, revealing that non-coding genes, once thought of as transcriptional "junk", are instead important regulators of protein-coding gene activity and play a crucial role in many biological and cellular processes [1,3]. Accordingly,

* Corresponding author. Department of Biomedical Sciences, University of Sassari, Viale San Pietro 43B, 07100, Sassari, Italy.
** Corresponding author.
E-mail addresses: gpintus@uniss.it (G. Pintus), hatem.zayed@qu.edu.qa (H. Zayed).
[1] Equal contribution.

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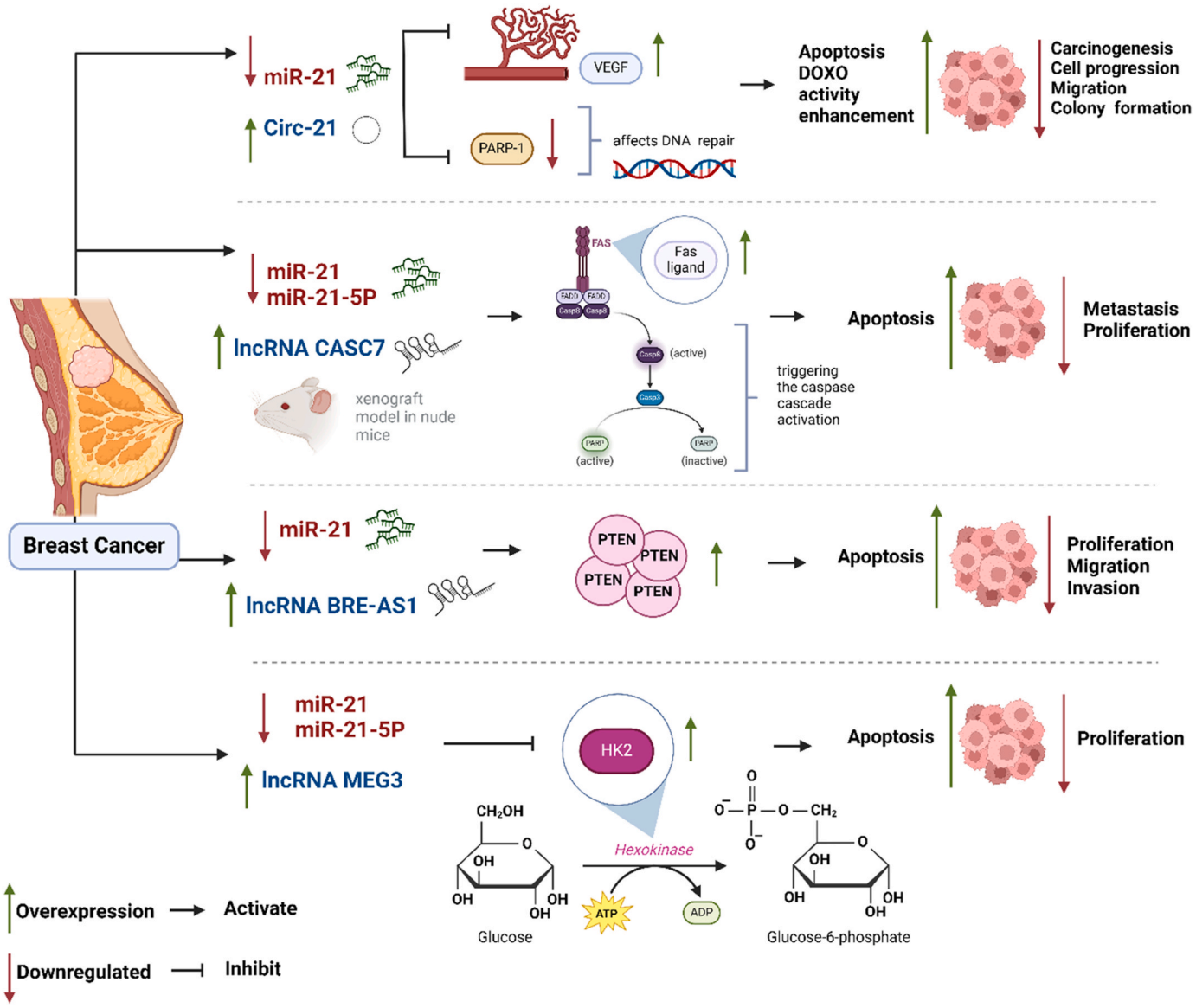

Fig. 1. The figure illustrates the mechanisms associated with miR-21 downregulation, which enhances breast cancer apoptosis and inhibits cancer progression and metastasis.

pathophysiological implications of various diseases are strongly associated with non-coding transcriptome abundance, thus strengthening the relevance and impact of non-coding genes [4]. Based on their size, non-coding RNAs (ncRNAs) are classified into two categories: small ncRNAs (sncRNAs) and long ncRNAs (lncRNA). The former includes non-coding transcripts with less than 200 nucleotides to which belong: a) microRNAs (miRNAs) that destabilize and inhibit the mRNA translation by binding to its 3′UTR at the RNA level. [5], b) small interfering RNAs (siRNAs) [5,6], c) transfer RNAs (tRNAs) [7], and d) piwi-interacting RNAs (piRNAs) [8,9]. Non-coding transcripts of over 200 nucleotides are known as lncRNAs. They can be intergenic, antisense, or intronic in relation to protein-coding genes [10]. They contain 5′-caps and 3′-poly-A tails but don't have protein-coding potential [10]. lncRNAs exhibit various functions, including chromatin structure modulation, nuclear organization, and gene regulatory potential at both transcriptional and post-transcriptional levels [11,12]. Furthermore, they can also function as guides, scaffolds, decoys, and enhancer RNAs [13]. Circular RNAs (circRNAs), a novel subclass of lncRNA with a covalent closed circular structure lacking a 5′ end cap or 3′ poly (A) tail, also belong to this group [14]. Similarly to lncRNA, the biological roles of circRNAs range from post-transcriptional regulators to protein scaffolds and miRNA sponges [15,16]. As mentioned above, miRNAs are considered one of the most evolutionary conserved and abundant classes of sncRNAs [5]. The level of complementarity between miRNA and mRNA determines the employed silencing mechanism, which can either be the translation repression or mRNA cleavage; in both cases, the mRNA will not be translated into a functional protein [17]. miRNAs are involved in various biological and developmental processes, including cell proliferation, apoptosis, cell cycle control, immune responses, stem cell division, and metabolism [18,19]. As a result, a dysregulated miRNA expression is implicated in the pathogenesis of various diseases, including cancer, cardiovascular, diabetes, and autoimmune [20–24], and therefore, miRNAs can effectively be used as disease biomarkers [25–27] or druggable molecules [28–31].

With regard to malignancies, working as either tumor suppressors or oncogenes depending on the signaling pathways involved and altered expression of target genes, miRNAs play a crucial role in the development and progression of various human cancers [25,32–34]. Besides, several miRNAs can potentially be used as diagnostic, prognostic and therapeutic biomarkers in human cancers [25,32]. In this regard, one of

the earliest identified oncomiR is miR-21, which is usually overexpressed in various cancers, including glioma, colorectal, prostate, breast, and ovarian cancer [35–39]. One of the main mechanisms by which miR-21 accelerates cancer development is by affecting (e.g., by downregulating tumor suppressor genes) downstream signaling pathways involved in cell proliferation, survival, and invasion [35,40–43]. Similarly, miR-21 can also affect signaling pathways involved in autophagy, apoptosis, metastasis, and angiogenesis [44,45].

A further level of complexity in the regulatory mechanisms underpinning tumor development and progression is due to the role played by the interaction between lncRNAs and miRNAs. Indeed, acting as competing endogenous RNA (ceRNA), lncRNA inhibits the available miRNA from binding to the target mRNA, thus blocking its function, whether tumorigenic or antitumorigenic [46,47]. In other words, lncRNAs act as miRNA sponges, decreasing the miRNAs' regulatory effect on the downstream target genes [48]. An increasing number of studies showed that lncRNA-miRNA-mRNA regulatory axes are involved in several biological processes associated with tumorigenesis and tumor metastasis, such as cell proliferation, apoptosis, cell-cycle regulation, migration, invasion, epithelial-mesenchymal plasticity, and drug resistance [49–53]. In addition to the relevance and impact that these regulatory axes have on cancer pathophysiology, they also proved to be powerful diagnostic and prognostic tools. Given the key role of miR-21 in cancer development, progression, diagnosis, and therapy, the purpose of this work is to gather, analyze, and discuss the latest research progress on the regulatory association between miRNA-21 and lncRNAs in different types of human cancer and its pathophysiological implications.

2. Breast cancer

Breast cancer (BC) is the most common cancer in females and the leading cause of early mortality among women worldwide [54,55]; new cases of this cancer are indeed constantly increasing year by year [54]. Chemotherapy is the principal strategy for treating BC patients. However, the resistance to chemotherapy and the chemotherapy-associated side effects, which compromise the functionality of several organs, are the main barriers to BC treatment [55]. As mentioned above, miRNA-21 (miR-21) functions as an oncomiRNA, and its expression is associated with carcinogenic processes and drug resistance mechanisms in many cancer types [55,56]. A recent study illustrated that miR-21 overexpression is correlated to increased levels of the proangiogenic factor VEGF (vascular endothelial growth factor) and therapeutic resistance enhancement in HER2+ (positive human epidermal growth factor receptor 2) BC [55]. Furthermore, miR-21 overexpression causes poly [ADP-ribose] polymerase 1 (PARP-1) inhibition, affecting DNA repair and inducing apoptosis suppression. Mechanistically, a circular sponge (Circ-21) sequesters miR-21, and by decreasing its expression levels, carcinogenesis processes such as cancer cell progression, migration, and colony formation are suppressed [55]. In addition, both PARP-1 and VEGF protein expression resulted respectively increased and decreased by the action of circ-21. Interestingly, circ-21 also caused G2/M phase cell cycle arrest in the BC cell line MCF7 but not in the MCF10A cell line [55]. Concerning the chemotherapy resistance, circ-21 was able to increase the DOXO activity concomitantly with the decreased gene expression of the resistance genes ABCA1, ABCC4, and ABCC5 (Fig. 1) [55]. Also, the lncRNA CASC7 (cancer susceptibility candidate 7 lncRNA) has recently been shown to act as a BC suppressor through the miR-21-5p/FASLG axis regulation [54]. CASC7 is downregulated in both BC tissue and cells, while CASC7 overexpression suppresses BC growth and metastasis [54]. In addition, CASC7 overexpression results in the elevation (both at gene and protein level) of Fas ligand (FASLG), a member of the tumor necrosis factor superfamily, whose primary role is the triggering the caspase cascade activation initiating apoptosis through FAS binding [57,58]. These findings, further verified *in vivo* using a xenograft model in nude mice, highlight that CASC7 plays a tumor-suppressive role in BC by inhibiting miR-21 oncogenic effect and raising FASLG levels (Fig. 1) [54].

Triple-negative breast cancer (TNBC) is a subtype of BC that misses progesterone (PR) and estrogen receptor (ER) expression and lacks the human epidermal growth factor receptor-2 (HER2) overexpression [59]. Within this framework, miR-21 was shown to promote proliferation and invasion of TNBC cells by targeting the oncosuppressor protein phosphatase and tensin homolog (PTEN) (Fig. 3) [60]. On the other hand, lncRNA BRE-AS1, recently recognized as a tumor suppressor in prostate carcinoma and lung cancer [61,62], inhibits TBNC proliferation by downregulating miR-21 [56]. Specifically, BRE-AS1 and miR-21 showed opposite expression profiles that were also significantly correlated with poor survival of TNBC patients; indeed, the former resulted decreased, while the latter was significantly higher in TNBC patients than healthy subjects [56]. Furthermore, BRE-AS1 overexpression inhibited proliferation, migration, and invasion of TNBC cells by increasing the expression levels (both at gene and protein levels) of PTEN while decreasing those of miR-21. Conversely, overexpression of miR-21 enhanced proliferation, migration, and invasion of TNBC cells but showed no effect on BRE-AS1 expression (Fig. 1) [56].

2.1. MEG3 lncRNA

Maternally expressed gene 3 (MEG3) is another lncRNA with an opposite expression pattern compared to miR-21 in BC tissues and cells [63]. MEG3 overexpression was shown to inhibit BC tumorigenesis by suppressing cell proliferation and promoting apoptosis [63]. Besides, MEG3 has also been shown to suppress the expression of hexokinase 2 (HK2), the enzyme responsible for glucose-6-phosphate (G6P) production in the glucose metabolic pathway [63]. High glycolysis is indeed a common biochemical feature of cancer cells since it is essential for their growth and survival [64]. Luciferase reporter assay, RNA immunoprecipitation chip (RIP) assay, and qRT-PCR analysis collectively revealed that MEG3, acting as a sponge of miR-21, negatively regulates HK2 expression [63]. Accordingly, MEG3 overexpression inhibits miR-21-mediated PI3K/Akt pathway activation, ultimately leading to BC tumorigenesis inhibition (Fig. 1) [63].

3. Cervical, endometrial and ovarian cancer

3.1. Cervical cancer

Cervical cancer (CC) is a mortality-causing gynecological cancer among women worldwide [65,66]. About 500 thousand CC new cases are reported yearly [67]. Squamous cell carcinoma (CSCC) is the most prevalent type of CC, accounting for 90% of the total cases [68]. Early detection of CC can positively influence treatment for patients who may undergo radical surgery. In contrast, the late detection of patients with CC advanced stages leads to poor prognosis due to a lack of efficient treatment [68]. Chemotherapy is the gold standard protocol used to treat patients with large tumors or metastatic lesions, while cisplatin is the first-line chemotherapy drug used to treat ovarian cancer and CC [65,66]. However, late-stage patients have a poor prognosis because of developed resistance to the chemotherapy regimen [65,67]. Understanding chemoresistance molecular mechanisms in cervical cancer is thus crucial for the development of targeted therapies. Several studies proved oncogenic miR-21 is involved in CC, where it can target different tumor suppressors [69], as well as in cervical squamous cells, where it can induce tumorigenesis via the tumor growth promoter CCL20 (C–C Motif Chemokine Ligand 20) regulation [70]. Besides, several miR-21-lncRNA interactions have also been demonstrated in CC [65–67]. In this regard, a recent study investigated the function of lncRNA LOXL1-AS1 and its relationship with miR-21 in cervical squamous cell carcinoma (CSCC) [68]. Unlike other types of cancers, including prostate cancer and glioblastoma, where LOXL1-AS1 was found upregulated, in CSCC, this lncRNA resulted downregulated [68]. Besides, its overexpression decreased cell invasion and migration rates

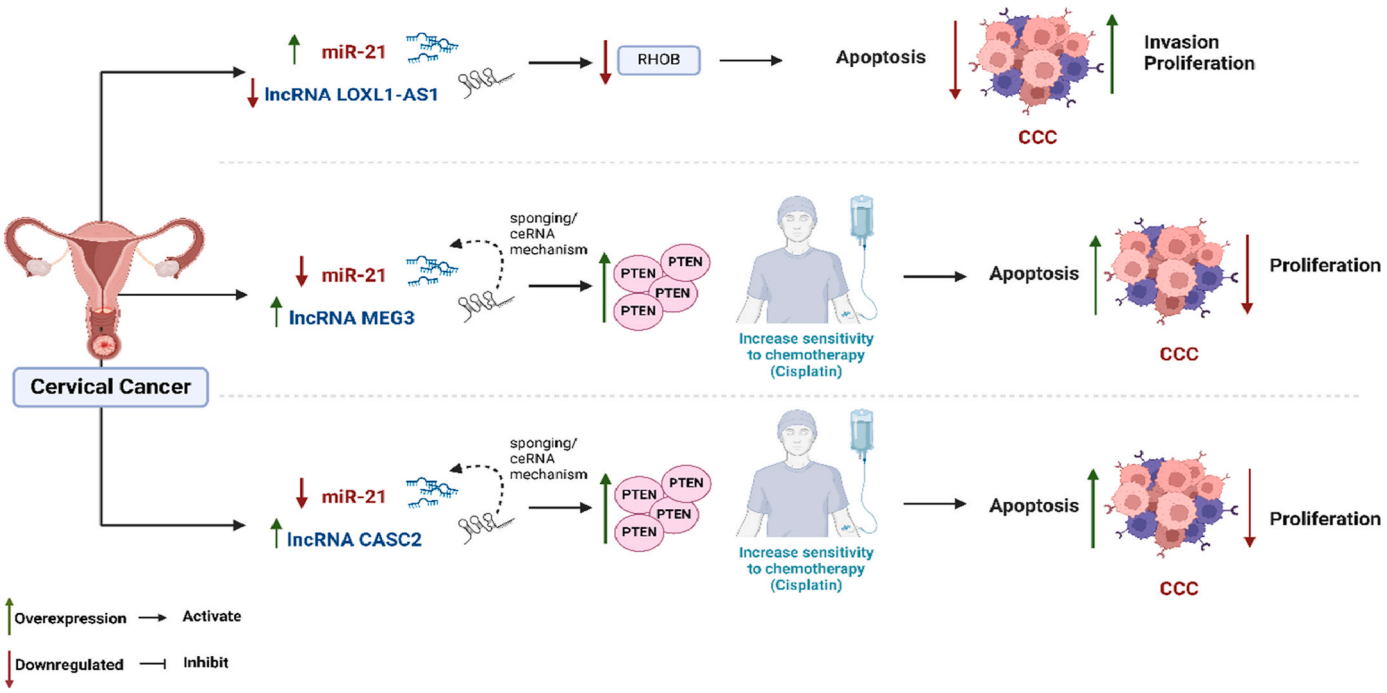

Fig. 2. The figure illustrates the effect of miR-21 downregulation and upregulation on cervical cancer progression and metastasis.

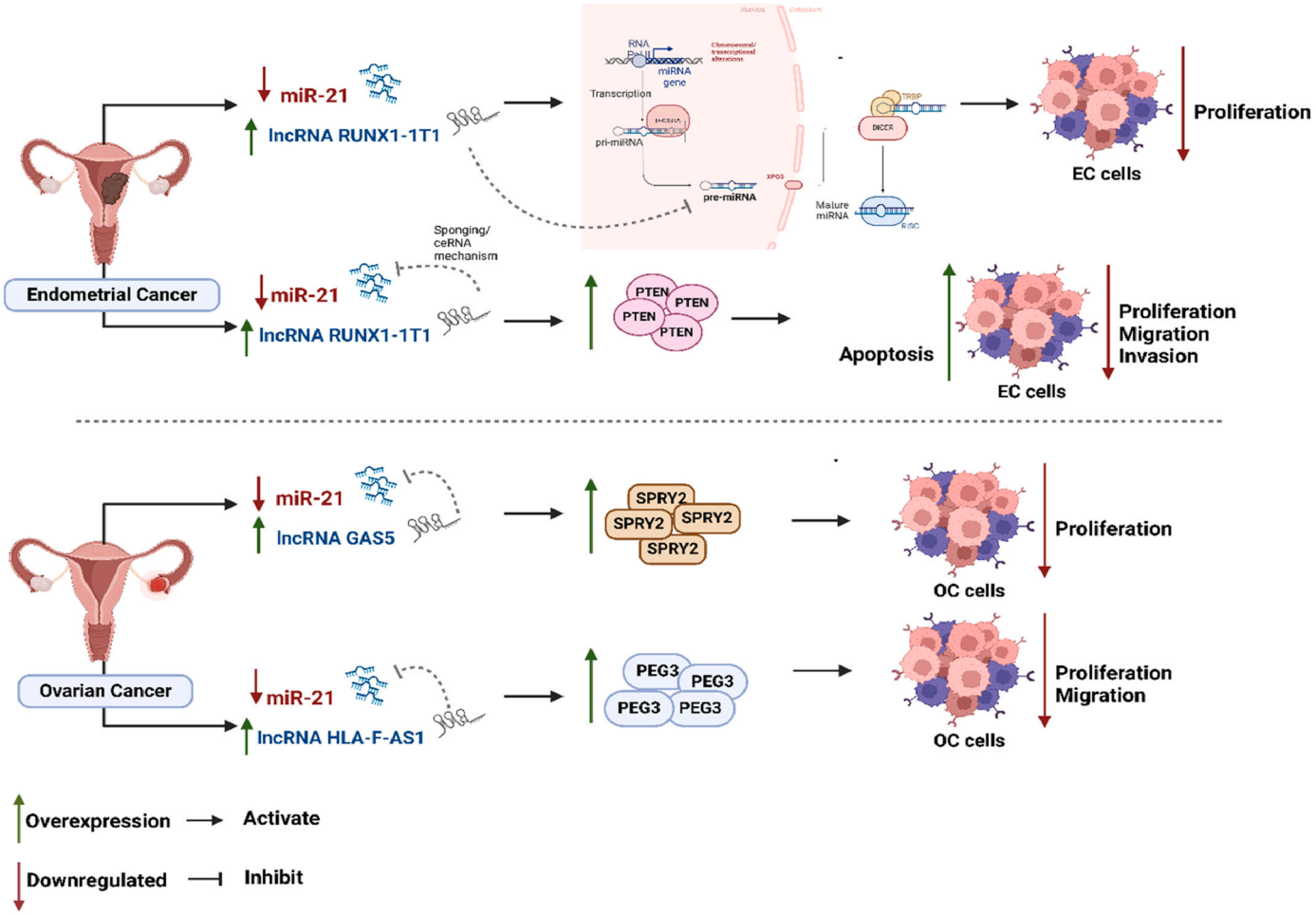

Fig. 3. The figure depicts the effect of miR-21 downregulation in both endometrial and ovarian cervical cancer, which inhibits cancer progression and metastasis.

of CSCC cells, indicating a tumor suppressor role. In silico analysis and dual luciferase assay suggested the potential interaction between LOXL1-AS1 and miR-21; however, LOXL1-AS1 overexpression had no effects on miR-21 expression, as miR-21 overexpression on the LOXL1-AS1 expression [68]. Instead, LOXL1-AS1 overexpression resulted in the upregulation of the tumor suppressor Ras Homolog Family Member B (RHOB), a direct target of miR-21 [68]. Similarly to LOXL1-AS1, overexpression of RHOB decreased invasion and migration rates of CSCC cells, while miR-21 mitigated the impact of LOXL1-AS1 and RHOB overexpression. These results collectively suggest that LOXL1-AS1 participates in CSCC by regulating the miR-21/RHOB axis (Fig. 2) [68].

3.1.1. MEG3 lncRNA

MEG3 is another differentially expressed lncRNA in CC; precisely, MEG3 was reported downregulated in CC tissues from 108 patients compared to the adjacent normal tissues [67]. Moreover, MEG3 expression resulted negatively correlated with clinicopathologic features of CC, such as tumor size, degree of tumor spread, lymphatic metastasis, and high risk-human papillomavirus (HR-HPV) infection [67]. In vitro experiments also demonstrated that MEG3 expression is linked to CC cell replication ability; indeed, MEG3 knockdown promoted cell proliferation and reduced apoptosis of CC cells, while MEG3 overexpression considerably enhanced apoptosis and arrested cell growth. Although the interaction between MEG3 and miR-21 in CC has not well established, the MEG3 expression was found to be negatively correlated with miR-21 expression; indeed, miR-21 downregulation resulted in MEG3 overexpression, whereas miR-21 upregulation resulted in MEG3 suppression [67]. These results collectively suggest that MEG3 may regulate miR-21 expression, consequently inhibiting CC cell proliferation and fostering apoptosis [67]. A recent study, besides confirming MEG3 downregulation in CC and its role as a tumor suppressor, also showed that MEG3, acting as ceRNA, promotes CC cells cisplatin sensitivity through the miR-21/PTEN axis regulation (Fig. 2) [66].

3.1.2. CASC2 lncRNA

Interestingly, the lncRNA, cancer susceptibility candidate 2 (CASC2), can also enhance cisplatin sensitivity by regulating CC cells' miR-21/PTEN axis [45]. Similarly to MEG3, CASC2 is low expressed in CC tissues and cells, and in cisplatin-resistant CC cells [65]; accordingly, CASC2 overexpression can inhibit CC cell viability and proliferation, whereas CASC2 downregulation can promote them [65]. Besides, CASC2 expression is inversely related to miR-21 expression and directly related to PTEN expression in cisplatin-resistant CC cells, as confirmed by both real-time PCR and Western blot experiments; also, as suggested by luciferase assays, miR-21 directly binds CASC2 [65]. Data collectively indicate that CASC2 functions as a ceRNA and inhibits miR-21 to promote PTEN and ultimately sensitize CC cells to cisplatin [65]. Both MEG3 and CASC2 are thus promising therapeutic candidates to use in combination with traditional cisplatin-based chemotherapy for CC treatment (Fig. 2) [65,66].

3.2. Endometrial cancer

Endometrial cancer (EC) is the most common gynecologic cancer with an incidence strongly associated with advanced age and obesity [71,72]. Although EC diagnosis and therapy improved significantly, treatments have multiple side effects, including infertility; besides, 15%–20% of patients have recurrence and metastasis in ovaries, vagina, bladder, and rectum [71,72]. Understanding the molecular strategies involved in EC progression is thus essential to enhance EC therapeutic agents' effectiveness. In this regard, emerging studies demonstrated that lncRNAs contribute to EC development and progression through different mechanisms [73]. An increasing number of lncRNAs are aberrantly expressed in EC tissues, and some of them have shown promising diagnostic and prognostic potential [74]. On the other hand, miR-21 has an important diagnostic value in EC, and its differential expression is associated with clinicopathological parameters. For instance, higher miR-21 expression is associated with advanced disease stage, as per the International Federation of Gynecology and Obstetrics (FIGO) classification, as well as with cervical invasion, myometrial invasion and distant metastasis [75,76]. Accordingly, some miR-21-lncRNA interactions have been reported as important checkpoints of EC cell proliferation, metastasis and apoptosis [77,78]. This is the case of the relationship between lncRNA RUNX1-1T1 and miR-21 [77], where RUNX1-1T1, which is downregulated in EC, acts as a tumor suppressor and decreases EC cell proliferation by suppressing miR-21 activity. Precisely, RUNX1-IT1 suppresses miR-21 maturation by interacting with miR-21 precursor (Fig. 3) [77]. This mechanism is suggested by expression analysis results showing that the RUNX1-1T1 expression is inversely correlated with miR-21 but not with miR-21 precursor; also, RUNX1-1T1 overexpression downregulates mature miR-21 (resulting in EC cells proliferation decreasing), but not miR-21 precursor. Finally, dual-luciferase activity assay and RNA pull-down assay confirmed the predicted interaction between RUNX1-IT1 and miR-21 precursor [77]. The interaction between lncRNA NBAT1 and miR-21-5p has also been described in EC. Precisely, NBAT1 enhances PTEN expression by sponging miR-21-5p to ultimately repress EC cell proliferation and promote apoptosis [78]. Therefore, similarly to RUNX1-1T1, NBAT1 acts as a tumor suppressor and is downregulated (whereas miR-21 is upregulated) in EC. Overexpression of NBAT1 inhibits EC cell proliferation, migration, and invasion; it also induces apoptosis and increases PTEN expression at both gene and protein levels. Opposite effects are instead observed with miR-21-5p overexpression (Fig. 3) [78].

3.3. Ovarian cancer

Ovarian Cancer (OC), the malignancy of the ovaries, is the fifth leading cause of death in women due to its advanced stage at diagnosis [79]. In recent decades, various lncRNAs have been shown to play a part in OC pathophysiology, mainly as tumor suppressors [80]. For instance, lncRNA HLA-F Antisense RNA 1 (HLA-F-AS1) was shown to suppress OC development by targeting the miR-21-3p/Paternally Expressed 3 (PEG3) axis [81]. PEG3 is targeted by miR-21, which in turn is targeted by HLA-F-AS1; indeed, HLA-F-AS1's overexpression attenuates the miR-21-induced increases of OC cell proliferation and migration, whereas PEG3 overexpression abolishes the miR-21-induced cancer progression [81]. Overall, both *in vivo* and *in vitro* data have shown the HLA-F-AS1mediated attenuation of OC development and progression via the miR-21-3p/PEG3 axis (Fig. 3) [81].

3.3.1. GAS5 lncRNA

Similarly to the role played in colorectal [82] and lung cancer [83], GAS5 functions as a tumor suppressor in OC. In OC cells, GAS5 is downregulated, while GAS5 overexpression results in inhibition of OC cell proliferation [80]. The underlying mechanism of this inhibition involves miR-21 and Sprouty homolog 2 (SPRY2), a member of the Sprouty family with a tumor suppressive role in OC [84]; indeed, patients with low SPRY2 expression show poorer prognosis than those with high SPRY2 expression [85]. MiR-21 is a target gene of GAS5, and SPRY2 is a target gene of miR-21 [80]; accordingly, overexpression of GAS5 decreases miR-21 expression and increases SPRY2 expression, in addition to inhibiting OC cell proliferation. On the contrary, miR-21 overexpression results in decreasing SPRY2 expression and attenuation of GAS5 suppressive effects on OC proliferation [80]. SPRY2 is thus a downstream effector of GAS5/miR-21 signaling in OC cells; precisely, GAS5 suppresses OC cell proliferation by inhibiting miR-21 expression and consequently increasing SPRY2 expression (Fig. 3) [80].

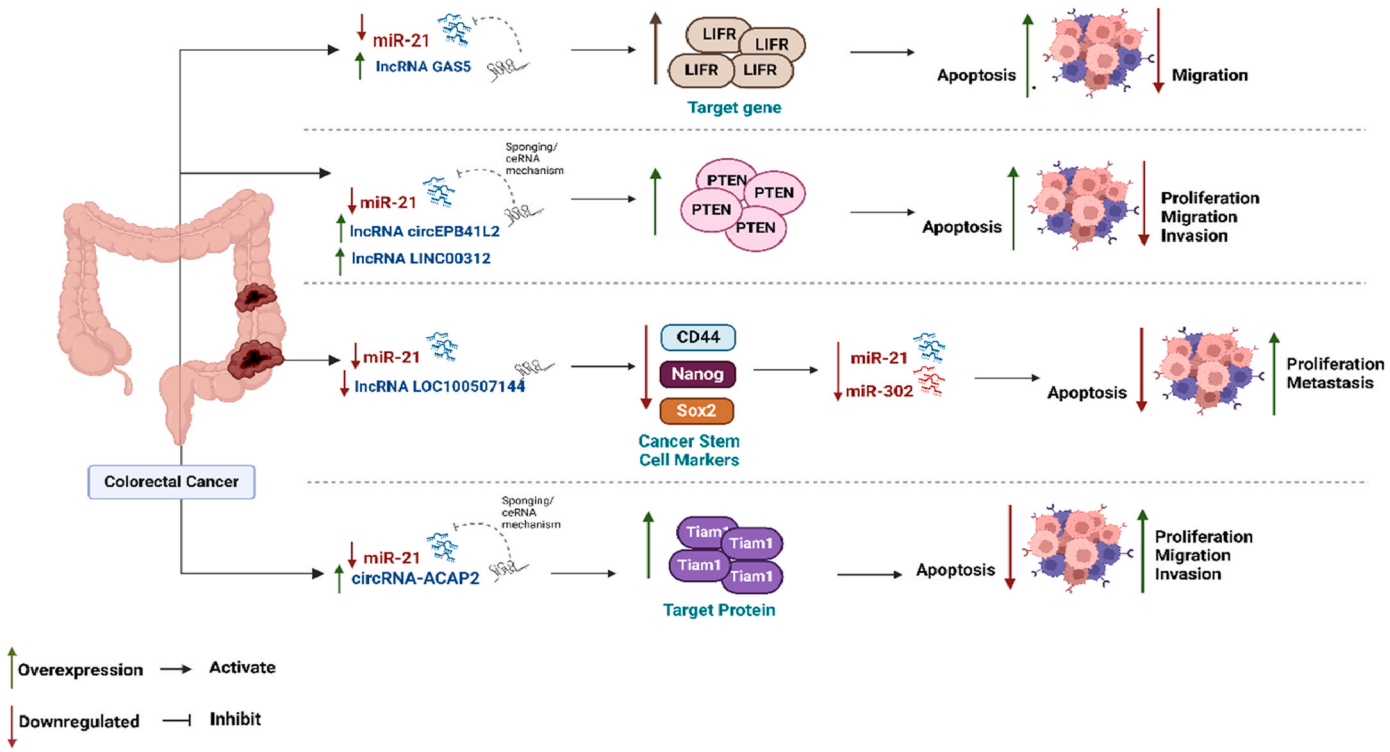

Fig. 4. The figure illustrates four mechanisms that affect colorectal cancer progression and metastasis via the interaction between the miR-21 axis and some lncRNAs.

4. Colorectal cancer

Colorectal cancer (CRC) is a malignant tumor of the colon and rectum cells. It is the third most common death-causing cancer worldwide, and its incidence in younger adults has dramatically increased in the last decade [86]. Surgery is the primary treatment in patients with early diagnosis, followed by chemotherapy and radiotherapy. Nonetheless, the survival rate is still low because of reoccurrence and metastasis [86]. Consequently, investigating the molecular mechanisms of CRC onset and progression is highly demanded to recognize important biomarkers for diagnostic and therapeutic purposes. In this regard, the molecular pathways involving lncRNA-miRNA interaction may provide a novel diagnostic and therapeutic approach to CRC.

4.1. GAS5 lncRNA

Similarly to what was reported in OC [80], the interplay between lncRNA GAS5 and miR-21 has a key role in CRC progression [82]. Precisely, GAS5 expression is inversely correlated with miR-21 expression in CRC cells, and their interaction reciprocally affects their role in CRC. CRC cells display lower expression levels of GAS5 than normal cells, resulting in increased tumorigenesis and a low survival rate. Besides, GAS5 knockdown boosts cell viability inhibits apoptosis and stimulates cell migration. Conversely, GAS5 overexpression suppresses miR-21 expression, promotes cell apoptosis and suppresses cell migration [82]. Moreover, acting as ceRNA, GAS5 competitively binds miR-21 and blocks its inhibitory action on the target gene leukemia inhibitory factor receptor (LIFR) (Fig. 4). Therefore, by targeting the miR-21/LIFR axis, GAS5 may suppress proliferation and metastasis of CRC and provide a potential target for CRC treatment [82]. Exosomes are extracellular vesicles containing proteins, bioactive lipids, and RNAs (including miRNAs, lncRNAs, and circRNAs) acting as intercellular messengers [87].

4.2. Other lncRNAs

In the context of CRC growth and progression, some exosomal circRNAs were shown to play a regulatory role [88–90]. This is the case of circEPB41L2, which, acting as a sponge of miR-21 and miR-942-5p, represses CRC progression via the PTEN/AKT signaling pathway [90]. CircEPB41L2 is downregulated in plasma exosomes from CRC patients and cells, whereas its overexpression enhances apoptosis and inhibits the proliferation, migration, and invasion of CRC cells [90]. Also, exosomal circEPB41L2 inhibits the expression of miR-21-5p, miR-942-5p, and PTEN/AKT signaling pathway [90], whose activity is crucial for CRC progression [91,92]. This inhibitory role on CRC tumor growth has also been confirmed *in vivo* experiments, where the subcutaneous injection of exosomal circEPB41L2 in mice has significantly reduced tumor volume and weight (Fig. 4) [90]. MiR-21–PTEN axis resulted also regulated by LINC00312, another lncRNA with a tumor suppressive role in CRC. LINC00312 is indeed downregulated in both CRC tissues and cells, while its overexpression (or miR-21 inhibition) suppresses CRC cell proliferation, invasion, and migration [93]. Overall, LINC00312 can modulate CRC cell malignancy by suppressing the miR-21- PTEN axis (Fig. 4) [93]. A tumor suppressive role in CRC has also been described for lncRNAs DiGeorge syndrome critical region gene 5 (DGCR5), which was showed to inhibit CRC cells proliferation by downregulating miR-21 [94], and for cancer susceptibility candidate 2 (CASC2), whose expression level resulted inversely correlated with mir-21 levels [95]. However, the molecular mechanisms underpinning the relationship of these two lncRNAs with miR-21 still need to be fully understood. On the contrary, some lncRNAs associated with miR-21 have also shown an oncogenic function in CRC; is this the case of LOC100507144, whose expression resulted higher in advanced CRC stages, lymph node metastasis, and vascular invasion [96]. LOC100507144 gain-of-function experiments demonstrated that this lncRNA participates in CRC cell proliferation by restraining apoptosis and cellular senescence and promoting cell cycle progression [96]. Besides, LOC100507144 suppression inhibited the expression of key cancer stem cell markers, such as CD44, Nanog, and Sox2, as well as the expression of their targets, miR-302 and

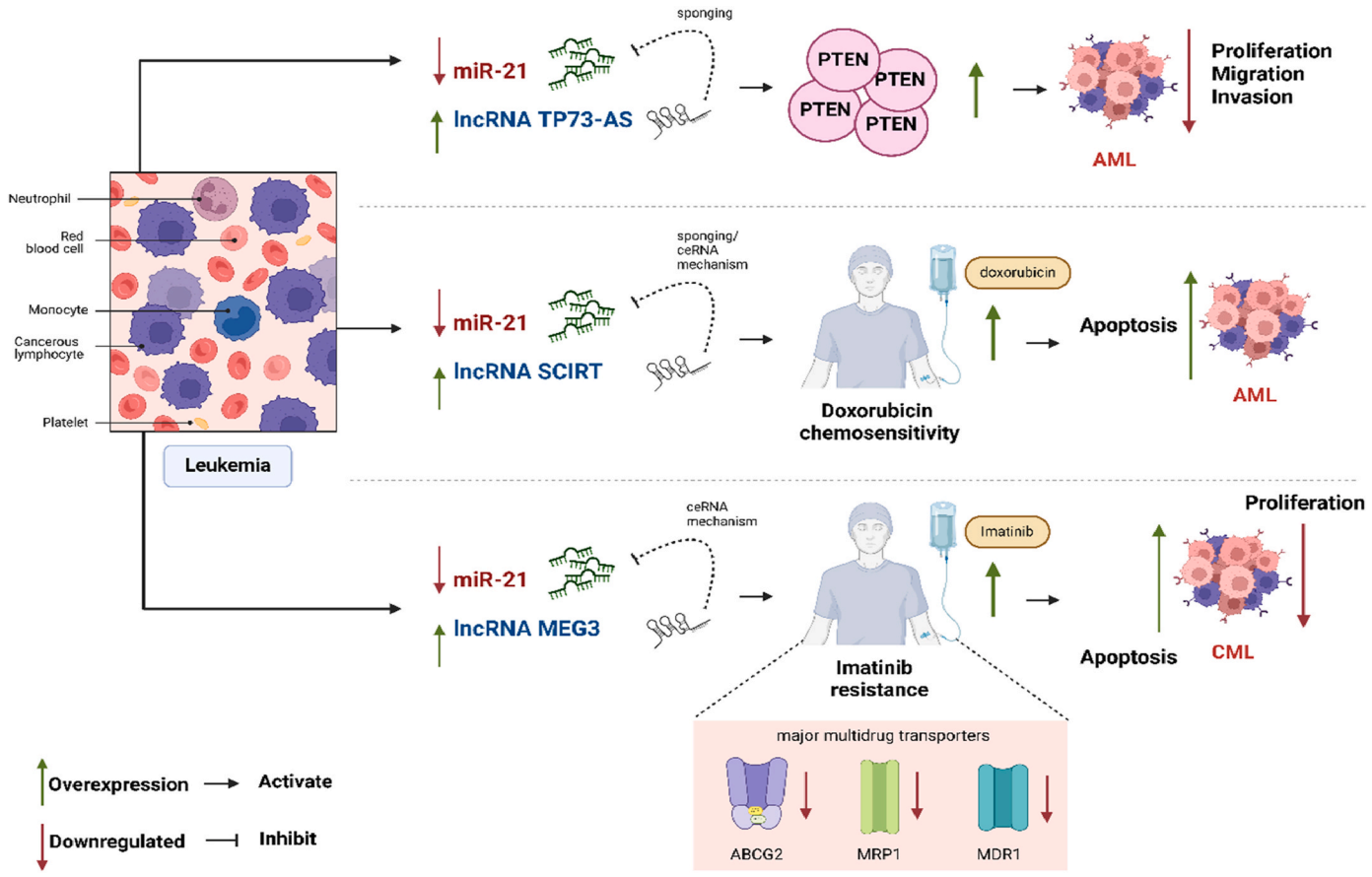

Fig. 5. The figure illustrates the interplay effect between the miR-21 axis and the lncRNAs TP73-AS, SCIRT, and MEG3 on leukemia cancer development and cancer drug resistance.

miR-21. Collectively, data suggest that LOC100507144 may enhance CRC progression and metastasis via the CD44/Nanog/Sox2/miR-302/miR-21 axis regulation (Fig. 4) [96]. Similarly, lncRNAs MALAT1 and circRNA-ACAP2, which are highly expressed in CRC tissues and cells, act as oncogenes by directly targeting miR-21 [97,98]. Specifically, MALAT1 inhibition was shown to prevent CRC cell invasion and migration, ultimately reducing tumor formation in tumor-bearing mice [97]. On the other hand, circRNA-ACAP2 acts as a miR-21 sponge to regulate T lymphoma invasion and metastasis protein 1 (Tiam1) expression, a protein associated with the tumor metastatic potential [98,99]. Similarly to circRNA-ACAP2, Tiam1 expression was found to be high in CRC tissue and cells and inversely correlated with miR-21 expression [98]. Accordingly, when circRNA-ACAP2 and Tiam1 expression was decreased, and miR-21-5p was increased, CRC cells proliferation, migration and invasion were suppressed, suggesting a regulatory role of circRNA-ACAP2/hsa-miR-21-5p/Tiam1 axis in CRC growth and progression (Fig. 4) [98].

5. Leukemia

Leukemia is a cancer of white blood cells. This cancer is clinically categorized into four categories, myeloid or lymphoid, and acute or chronic, in order to facilitate the treatment approach choice [100]. Acute myeloid leukemia (AML) is the most common type. With the advancement of cancer remedies, the survival rate of younger patients increased, but older patients still have poor prognoses and low survival rates [101]. Consequently, understanding the disease's molecular mechanism is highly demanded in order to find innovative diagnostic and therapeutic approaches. As mentioned above, lncRNAs play a critical regulatory role in cancer disease, either as tumor suppressors or oncogenes. In the context of AML, unlike other cancers, such as breast, lung, liver and esophageal cancer, lncRNA TP73-AS is downregulated and acts as a tumor suppressor by directly interacting with miR-21 [101]. Accordingly, AML cell proliferation, migration, and invasion are suppressed when TP73-AS is overexpressed, while the tumor suppressor and target of miR-21, PTEN, is upregulated. Collectively, these data indicate that TP73-AS1 may affect cell proliferation in AML by sponging miR-21 to upregulate PTEN (Fig. 5) [101]. SCIRT is another downregulated lncRNA in AML, as well as in doxorubicin-resistance (DR) AML patients, whereas miR-21 resulted upregulated [102]. SCIRT directly interacts with miR-21 but does not affect its expression. However, SCIRT suppresses the miR-21 inhibitory effect on doxorubicin-induced apoptosis, suggesting a ceRNA mechanism where SCIRT increases doxorubicin chemosensitivity by sponging miR-21 [102].

5.1. *MEG3 lncRNA*

Resistance to the chemotherapy drug Imatinib is one of the major problems in the treatment of chronic myeloid leukemia (CML), another common type of leukemia (Fig. 5) [103]. In this regard, lncRNA MEG3 was shown to contribute to Imatinib resistance by suppressing miR-21 expression [104]. Specifically, MEG3 resulted significantly downregulated in both blood samples of Imatinib-resistant CML patients and imatinib-resistant K562 cells. In these last, MEG3 overexpression reduced cell proliferation, promoted apoptosis, and increased Imatinib resistance, as well as reduced the expression of three major multidrug transporters, multidrug resistance1 (MDR1), multidrug resistance protein 1 (MRP1), and ATP-binding cassette transporter G2 (ABCG2). Moreover, MEG3 expression resulted negatively correlated with miR-21

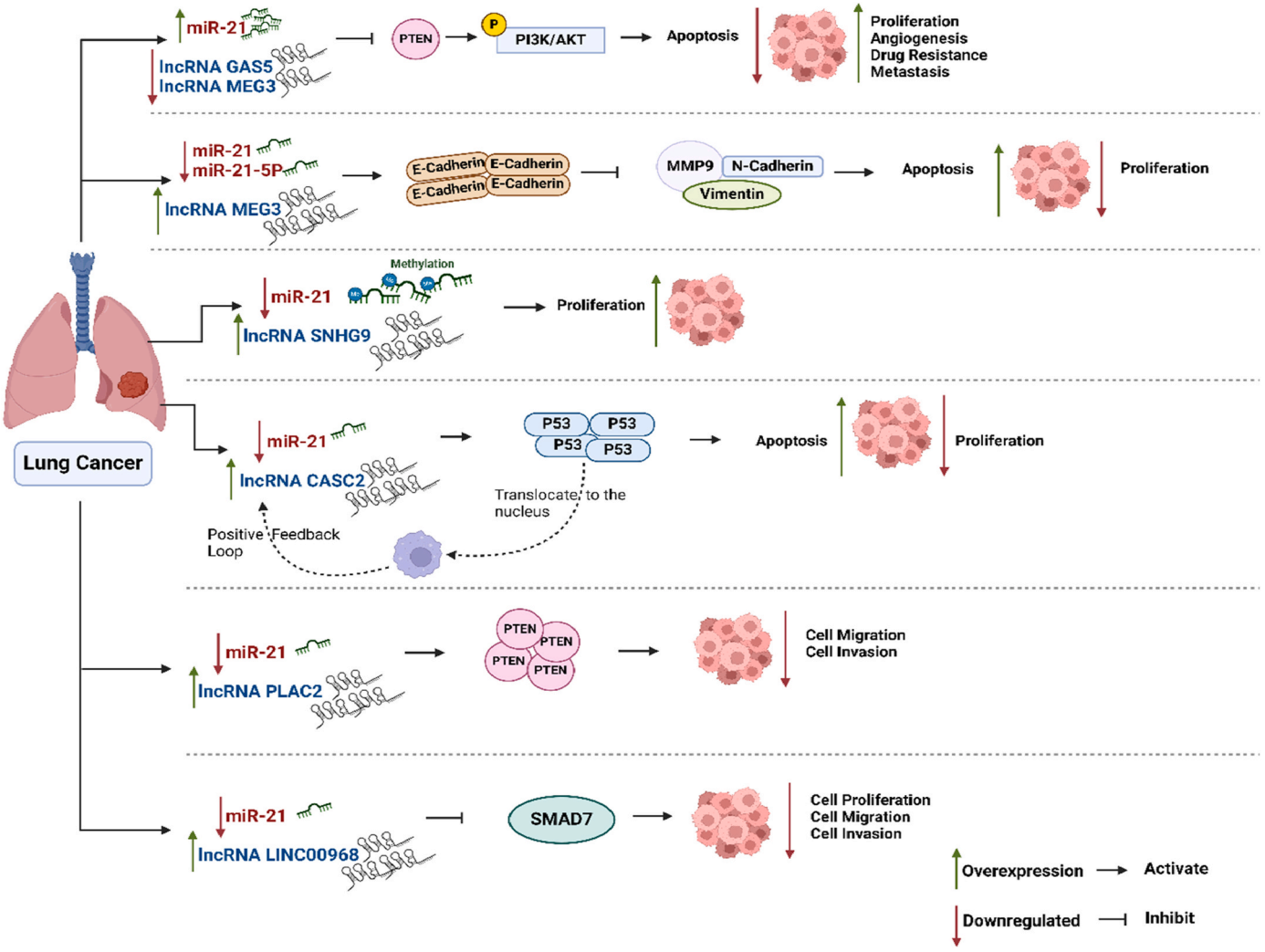

Fig. 6. The figure depicts the effects and molecular mechanisms of different miR-21-lncRNA axes in modulating lung cancer progression and metastasis.

in CML patients, while luciferase reporter assays indicated a potential interaction between MEG3 and miR-21. Taken together, these results suggest that MEG3 may regulate imatinib resistance in CML by acting as a ceRNA of miR-21 (Fig. 5) [104].

6. Lung cancer

Lung cancer or bronchogenic carcinoma refers to tumors originating in the lung parenchyma or within the bronchi. Since 1987, lung cancer has ranked among the top reasons for cancer-related deaths in the USA, also causing more female deaths than breast cancer [105]. The two main types of lung cancer are small-cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC), which currently account for 15% and 85%, respectively, of new lung cancer diagnoses [105]. Based on histological and clinical variations, NSCLC is further divided into three subtypes: adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma [106]. One of the most promising areas for developing future lung cancer treatments is gene therapy, and in this area, miRNAs are emerging as potential diagnostic biomarkers and therapeutic targets [107]. In this context, miRNA expression profiles that are able to distinguish between normal and malignant tissues, as well as tumor types, have been developed [107]. Besides, miRNA-based biomarkers allow the assessment of a patients' prognosis, responsiveness to chemotherapy, treatment effectiveness, and disease susceptibility and may represent powerful tools in lung cancer therapy [107]. In this context, miR-21 represents a valid diagnostic and prognostic biomarker in different tumors, including NSCLC [108–110]. miR-21 expression levels are indeed raised in NSCLC, and they are negatively correlated with patients' overall survival, supporting the oncogenic role of this miRNA [111–113].

6.1. *GAS5 lncRNA*

Based on the Cancer Genome Atlas (TCGA) dataset analysis, miR-21 expression in NSCLC cells is inversely correlated with the expression of the lncRNA, small nucleolar RNA host genes (SNHG9); similarly, they have opposite effects in NSCLC cells proliferation, as promoter or inhibitor for miR-21 and SNHG9 respectively [114]. Further analysis demonstrated a direct interaction between miR-21 and SNHG9; besides, SNHG9 overexpression strongly inhibited miR-21 expression (whereas miR-21 overexpression had no effect on SNHG9 expression), promoted the methylation of miR-21, and attenuated the increase of miR-21-induced NSCLC cells proliferation (Fig. 6) [114]. With the aim to investigate the molecular mechanisms underlying the radiosensitivity of NSCLC, a recent study demonstrated that the lncRNA GAS5 and the miR-21/PTEN/Akt axis play a key role in this process [115]. In particular, GAS5 expression in two NSCLC cell lines, NCI–H460 and A549, resulted associated with their different resistance to radiotherapy; indeed, NCI–H460 cells were more sensitive) to ionizing radiation (IR)-induced apoptosis than A549 cells and GAS5 was significantly

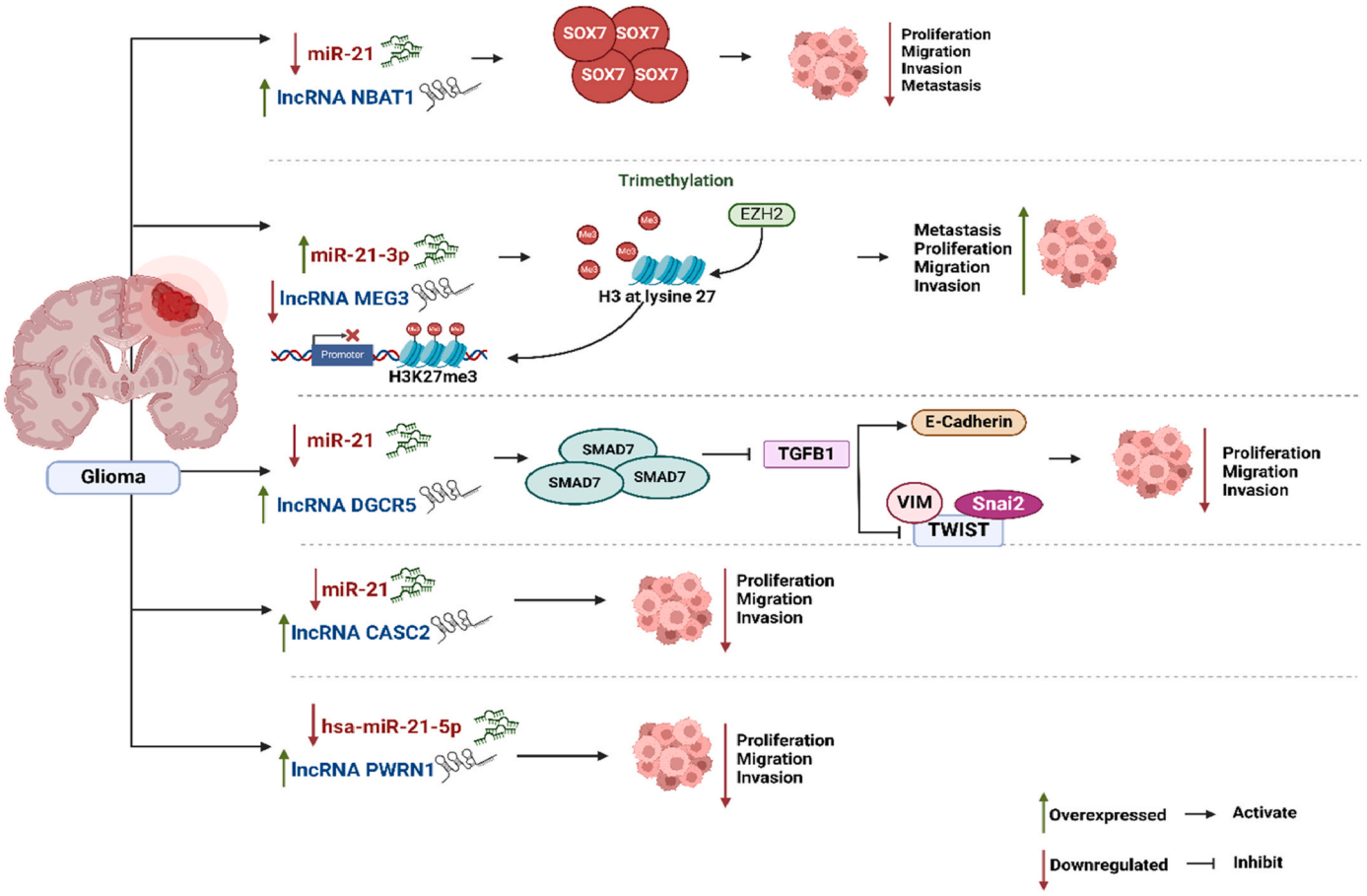

Fig. 7. The figure depicts the effects and molecular mechanisms of different miR-21-lncRNA axes in modulating glioma cancer progression and metastasis.

upregulated in NCI–H460 cells but not in A549 cells exposed to IR [115]. Overexpression of GAS5 decreased the miR-21 expression, and this inhibitory effect was significantly increased during IR, suggesting that GAS5/miR-21 interaction may be IR-specific [115]. The tumor suppressor PTEN, which is also a miR-21 target, is an inhibitor of the PI3K/Akt signaling pathway, a key pathway in IR-induced cell apoptosis [116]. In this regard, the interaction between GAS5 and the miR-21/PTEN/Akt axis was enhanced by IR. Specifically, GAS5 overexpression increased PTEN expression and decreased Akt phosphorylation through miR-21 modulation [115]. Resistance acquisition to cisplatin (DDP)-based chemotherapy is one of the major obstacles in NSCLC treatment [117]. In this regard, the ceRNA network, GAS5-miR-21-PTEN, where lncRNA GAS5 competes with PTEN for miR-21 binding, has been suggested to be involved in NSCLC sensitivity to DDP-based therapy [118]. GAS5, found downregulated in NSCLC patients, has been shown to suppress NSCLC cell proliferation and colony formation capacity and regulate their resistance to DDP through the PTEN pathway [118]. MiR-21 has instead opposite effects on NSCLC cell viability; indeed, according to previous studies [119], it promotes NSCLC cell proliferation, migration, and invasion and represses the activity of the tumor suppressive factor PTEN [120]. Results from in silico analysis, luciferase reporter gene assay, and immunoprecipitation suggested that GAS5 and PTEN share almost the same binding site for miR-21 and that GAS5 competes with PTEN for miR-21 binding [118]. This ceRNA mechanism also underpins NSCLC chemo-sensitivity to DDP through the PTEN pathway regulation; indeed, PTEN protein levels are decreased by GAS5 knockdown and increased by miR-21 inhibition [118]. Furthermore, under DDP treatment, NSCLC cell viability is promoted by GAS5 knockdown and suppressed by miR-21 inhibition; however, the effect of miR-21 inhibition on cell viability is partially counteracted by GAS5 silencing, indicating that the GAS5/miR-21 axis regulated NSCLC chemo-sensitivity to DDP through the PTEN pathway regulation (Fig. 6) [118].

6.2. *CASC2 lncRNA*

PTEN and miR-21 participate in a further regulatory network, which is always implicated in NSCLC cells-associated cisplatin cytotoxicity and involves the lncRNA cancer susceptibility candidate 2 (CASC2) [121]. It is known that CASC2 acts as a tumor suppressor in various tumors [122], and it is downregulated in almost all tumor types, including NSCLC [123]. Based on a recent study, CASC2 is also related to lung adenocarcinoma (LUAD) development, and it inhibits LUAD progression by forming a positive feedback loop with the miR-21/p53 axis [124]. Here, CASC2 inhibits miR-21 expression and increases p53 expression by targeting miR-21. P53, which acts as a transcription factor upstream of CASC2, can, in turn, activate CASC2 transcription [124].

6.3. *MEG3 lncRNA*

Similarly to the previously described role of GAS5 in the miR-21/PTEN/Akt regulatory network, the lncRNA MEG3 acts as a tumor suppressor by inhibiting NSCLC cell migration and invasion through the miR-21-5p/PTEN axis regulation (Fig. 6) [125]. MEG3, which is downregulated in NSCLC cells, inhibits NSCLC cell migration and invasion by sponging miR-21-5p, which in turn increases PTEN expression via the PI3K/AKT signaling pathway [125]. MEG3 can also inhibit the epithelial-mesenchymal transition (EMT) process; indeed, MEG3 overexpression significantly enhances both the transcript and protein levels of the endothelial marker E-cadherin and concurrently decreases the

mesenchymal markers, N-cadherin, Vimentin and MMP9 in NSCLC cells. MEG3 overexpression-induced effects were instead attenuated by miR-21-5p mimic [126]. These results are consistent with previous studies showing that MEG3 directly targets miR-21-5p and suppresses its expression, whereas miR-21-5p overexpression abolishes MEG3-induced inhibition of cell proliferation and apoptosis induction in NSCLC cells [127]. MEG3 was also shown to improve the cisplatin sensitivity of NSCLC cells via the miR-21-5p/SOX7 axis modulation [127]. Moreover, it was demonstrated that target sex-determining region Y-box 7 (SOX7) is a miR-21 direct target, and MEG3, acting as a ceRNA, suppresses the activity of miR-21-5p, releasing the inhibitory action that miR-21 exerts on SOX7 (Fig. 6) [127].

6.4. Other lncRNAs

A recent study highlighted that poor survival of NSCLC patients is associated with low tissue levels of the lncRNA PLAC2, which may thus represent a potential biomarker for NSCLC prognosis [128]. PLAC2 is an upstream inhibitor of miR-21, which in turn controls NSCLC cell invasion and migration by modulating downstream effectors of cancer-related pathways, such as the tumor suppressor PTEN. In this regard, PLAC2 overexpression resulted in PTEN upregulation, indicating that PLAC2 may relieve PTEN from miR-21-induced inhibition (Fig. 6) [128]. By combining lncRNA microarray data of LUAD tissues and cells from various online databases, such as Gene Expression Omnibus (GEO), TCGA, and the Atlas of Noncoding RNAs in Cancer (TANRIC), LINC00968 was found significantly downregulated in NSCLC [129]. To further validate this result, the effect of LINC00968 on NSCLC tumor growth and metastasis was evaluated both *in vitro* and *in vivo*. In particular, LINC00968 upregulation was shown to significantly inhibit cell proliferation, migration, and invasion. Label-free quantitative proteomics data indicated that LINC00968 overexpression affects the expression of key hippo signaling pathway effectors, especially SMAD7 [129]. Large-scale bioinformatics data mining revealed that the expression of both LINC00968 and SMAD7 was negatively correlated with miR-21-5p and that miR-21-5p was highly expressed in LUAD tissues and cells. Besides, miR-21-5p upregulation significantly promoted cell proliferation, invasion, and migration and partially attenuated the inhibitory effects of LINC00968 [129]. All these findings suggested that LINC00968 may serve as a ceRNA for miR-21-5p; therefore, by sponging miR-21-5p, it releases the inhibitory action of miR-21-5p on SMAD7 and enhances SMAD7 expression (Fig. 6) [129].

7. Glioma

Glioma is one of the most widely diagnosed brain malignancies in the central nervous system, with significantly high rates of mortality worldwide [130]. The observed poor prognosis is due to the high metastatic capability and strong invasiveness. Currently, the standard treatment for glioma involves surgery followed by postoperative combined radiotherapy and chemotherapy; however, patients' survival rate is less than 15 months [131,132]. Emerging studies demonstrated that several miRNAs-21-IncRNAs crosstalks are strongly associated with glioma cell proliferation and metastasis [133–139]. For instance, DGCR5 (similarly to the above-mentioned antiproliferative effect in CRC) was demonstrated to affect migration and invasion of glioma cells via the miR-21/Smad7 axis [140]. Regarding the underlying molecular mechanisms, it has been suggested that DGCR5 could inhibit miR-21 expression and, consequently, its inhibitory effect on Smad7 [140], which is a TGFβ1 signaling inhibitor able to repress TGFβ1-induced cancer EMT and metastatic ability [141]. Accordingly, DGCR5 overexpression was shown to reduce the mesenchymal markers VIM, Snai2, and TWIST and increase the epithelial marker E-cadherin, both at gene and protein levels [140]. On the other hand, miR-21 overexpression dramatically reversed the DGCR5 anti-tumor effect (Fig. 7) [140]. Similarly to what was described above in the context of EC, the tumor suppressive function of lncRNA NBAT1 and its relationship with miR-21 has also been reported in glioma by Guan et al. [142]. Specifically, the authors showed that NBAT1, which is downregulated in glioma tissues and cells and associated with poor prognosis, inhibits glioma cell proliferation, migration and invasion through the miR-21/SOX7 axis [142]. The miR-21-NBAT1 interaction, first predicted by in silico analysis, was also confirmed by dual-luciferase reporter assay; likewise, SOX7 was confirmed as a miR-21 downstream target. Besides, SOX7 expression level resulted lower in glioma tissues and cells as compared to paracarcinoma tissues and healthy astrocytes [142]. Overexpression of NBAT1 in human glioma cells (A172 and AM138) inhibited proliferation, migration, and invasion, increasing the SOX7 expression; opposite effects were instead observed with miR-21 mimics. Overall, data suggest the promising value of the NBAT1/miR-21/SOX7 axis as a therapeutic target for the treatment of glioma patients [142]. The LncRNA Prader-Willi region non-protein coding RNA 1 (PWRN1) has been reported to be aberrantly expressed in several cancers, including breast, prostate, and gastric cancers, but its expression in GBM was almost unknown [137,143]. A recent study found that PWRN1 is downregulated in both GBM tumors and GBM cell lines, and it suggested that PWRN1 may act as a suppressor of GBM tumors and cell lines via miR-21 inhibition [137]. This last showed instead to act as an oncogene in GBM [137]. In this context, a novel therapeutic approach involving exosomes packed with a miR-21-sponge construct has been recently developed [135]. These engineered exosomes delivered to GBM cells were able to decrease proliferation and elevate GBM cells' apoptotic rate; instead, administration of the modified exosomes in a GBM rat model led to a substantial reduction of tumor volume [135]. An important challenge in applying cell-based gene therapy to brain tumors is the blood-brain barrier (BBB) [135]. In this regard, it is noteworthy that engineered exosomes showed the potential to penetrate the BBB and efficiently transfer their contents in the brain (Fig. 7) [135].

Trimethylation of histone H3 at lysine 27 (H3K27me3) is an epigenetic modification to the DNA packaging protein, Histone H3, that acts as a transcriptional repressor of target genes (Fig. 7) [144,145]. H3K27 trimethylation is catalyzed by the methyltransferase Enhancer of Zester Homolog 2 (EZH2), an enzyme with a crucial role in cancer development and growth [144–146]. EZH2 is indeed aberrantly overexpressed in several tumors (e.g., prostate cancer, breast cancer, and ovarian cancer), where it promotes tumor growth and metastasis [146]. Moreover, mutations or altered functionality of this enzyme result in aberrant methylation or demethylation that can lead to malignancy [146]. In the context of glioma, EZH2 has been recently found to be overexpressed and linked to a reduced overall survival rate of glioma patients [125]. Besides, proliferation, invasion, and migration of glioma cells resulted markedly reduced when EZH2 was silenced, strongly suggesting its tumor promoter role. Of note, H3K27me3 expression was also significantly inhibited by EZH2 silencing [138].

7.1. MEG3 lncRNA

Mounting evidence indicates the role of lncRNAs, including MEG3, in the EZH2-regulated oncogenic processes [147]. In this regard, a study showed that MEG3 was downregulated in glioma cells, while EZH2 and miR-21-3p were upregulated; inhibition of EZH2, as well as MEG3 overexpression, restrained cell proliferation, migration, and invasion of U251 glioma cells, and an increase in the binding between H3K27me3 and the promoter region of MEG3 was also observed (Fig. 7) [138]. Overall, this study demonstrated that the EZH2-mediated H3K27me3 enrichment on the MEG3 promoter may affect the growth and metastasis of glioma cells by targeting miR-21-3p [138].

7.2. CASC2 lncRNA

CASC2, already described as tumor suppressor lncRNA in EC and CRC through targeting miR-21, was shown to similarly act in glioma

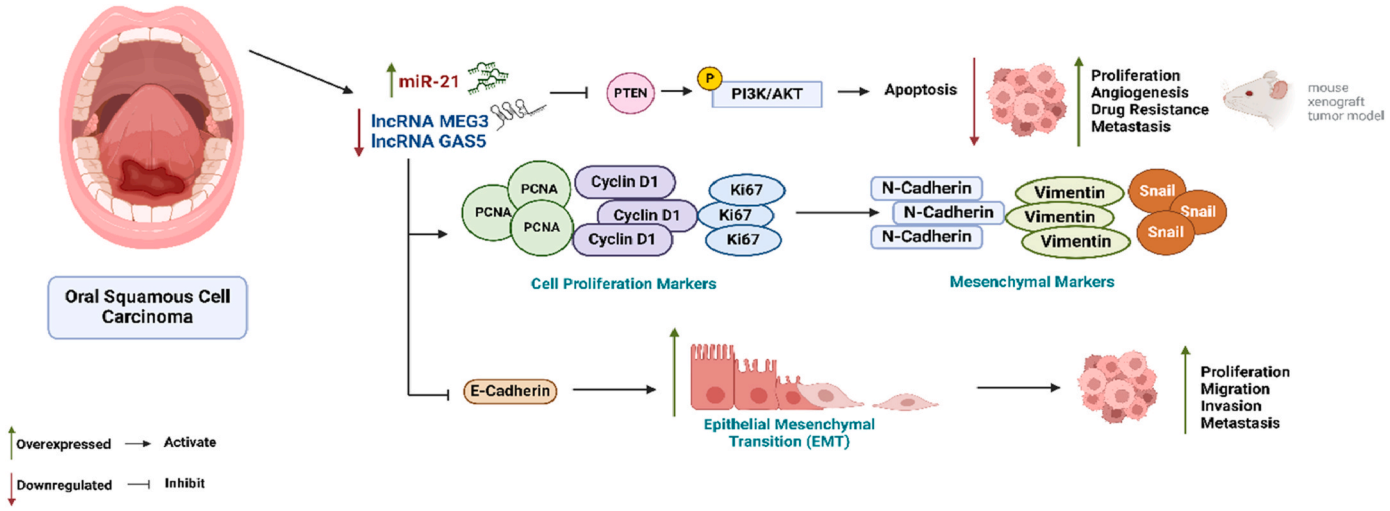

Fig. 8. The figure illustrates the effect of miR-21 overexpression on oral squamous cell carcinoma proliferation, metastasis, and drug resistance.

[139]. Here, CASC2 and miR-21 expressions and functions resulted negatively correlated both in glioma tissues and cell lines U251 and U87. CASC2 is indeed minimally expressed, and inhibits proliferation, migration, and invasion of glioma cells. miR-21 is instead overexpressed, and is responsible for glioma progression and malignancy [139]. Moreover, CASC2 is a target of miR-21 and the re is a reciprocal repression feedback loop between them [139]. Glioblastoma multiforme (GBM) is the most aggressive and malignant brain tumor; it is often diagnosed at late stages, and the survival rate is very low (Fig. 7) [148].

8. Oral, laryngeal and esophageal squamous cells carcinoma

8.1. Oral squamous cell carcinoma

Oral squamous cell carcinoma (OSCC) is the most prevalent type of head and neck cancer [149]. OSCC is thought to have caused 177,000 deaths and 377,000 new cases worldwide in 2023 [150]. Surgery is the main form of treatment for OSCC, followed by radiation or chemo-radiation therapy [151]. Despite treatment improvements, the five-year survival rate for OSCC is only 63%; this highlights the urgent need to better understand the molecular mechanisms behind OSCC pathophysiology and create more effective treatments [149]. Pseudogenes are DNA segments structurally resembling a gene but are non-functional in protein-coding [152]. They are usually located near the associated ancestral gene and play an important role in regulating gene expression [152]. Dysregulated pseudogenes are often associated with different human diseases and contribute to carcinogenesis [153]. Interestingly, a ceRNA mechanism where the pseudogene can competitively bind miRNAs to regulate the ancestral gene has also been shown [154]. In this regard, a recent study explored the relationship between PTEN and its pseudogene PTENp1 in OSCC [155]. Specifically, it was demonstrated that PTENp1, by sponging miR-21, mediates PTEN expression to inhibit OSCC cell proliferation and colony formation by triggering the cell cycle arrest through the AKT pathway [155]. QRT-PCR and western blotting analyses demonstrated that PTENp1 and PTEN expression levels were positively correlated but inversely correlated with miR-21 expression. This relationship between PTENp1 and PTEN expression was also confirmed in an OSCC mouse xenograft model (Fig. 8) [155].

8.1.1. GAS5 and MEG3 lncRNAs

The involvement of the GAS5/miR-21/PTEN axis, previously described as having a crucial role in the sensitivity of NSCLC to DDP-based therapy, has been recently reported in OSCC [156]. Here, the tumor suppressor role of GAS5 and the ceRNA mechanism whereby GAS5 modulates miR-21 and PTEN expression were also confirmed [156]. QRT-PCR and western blotting analysis showed that GAS5 knockdown led to the modification of several cell parameters, including a) increased expression of miR-21, b) increased expression of the cell proliferation markers proliferating cell nuclear antigen (PCNA), cyclinD1, and Ki-67, c) enhanced expression of the mesenchymal markers N-cadherin, vimentin, and snail 1), d) reduction of the epithelial marker E-cadherin, overall suggesting an increase of the EMT process (Fig. 8) [156]. OSCC progression has also been associated with lncRNA MEG3 activity in miR-21-associated fashion [157]. Indeed, the gene expression levels of MEG3 and miR-21 resulted in significantly lower and higher expression, respectively, in OSCC tissues compared to control tissues. In this context, dual luciferase assay suggested that MEG3 can selectively bind miR-21. In this regard, MEG3 overexpression showed the ability to inhibit cell proliferation and migration, whereas MEG3 knockdown showed opposite effects. Of note, miR-21 down-regulation reversed the effects associated with MEG3 overexpression [157].

8.2. Esophageal squamous cell carcinoma

Esophageal squamous cell carcinoma (ESCC) is a typical form of cancer without therapeutic cures [158]. ESCC incidence rate varies greatly worldwide, with China having the highest incidence rate [159]. Due to the lack of accurate and sensitive diagnostic indicators, ESCC is mostly diagnosed at advanced stages when metastases have already occurred, therefore resulting in poor prognosis [160]. This is why there is an urgent need for new prognostic and therapeutic indicators [161]. In the last decade, several miRNAs, including miR-21, have been found dysregulated in ESCC and shown to be potentially involved in its onset and progression [162]. Therapeutic strategies leading to miRNA loss-of-function may thus represent a valid strategy to modulate and eventually counteract tumor growth. In this regard, a synthetic circular RNA sponge has been engineered to achieve the loss-of-function of miR-21 and miR-93 [163]. Luciferase assays proved the ability of the artificial sponge to efficiently sequester endogenous miR-21 and miR-93 in a dose-dependent manner. Also, *in vitro* and *in vivo* functional experiments demonstrated that the synthetic sponge inhibits cell proliferation and migration, as well as tumor growth in a murine xenograft model [163]. In the context of ESCC, a recent study investigated the role of a newly discovered lncRNA imatinib-up-regulated (IUR) and its relationship with miR-21 [164]. IUR was found to be down-regulated and negatively linked with patient survival in ESCC; besides, IUR expression levels were positively correlated with PTEN mRNA

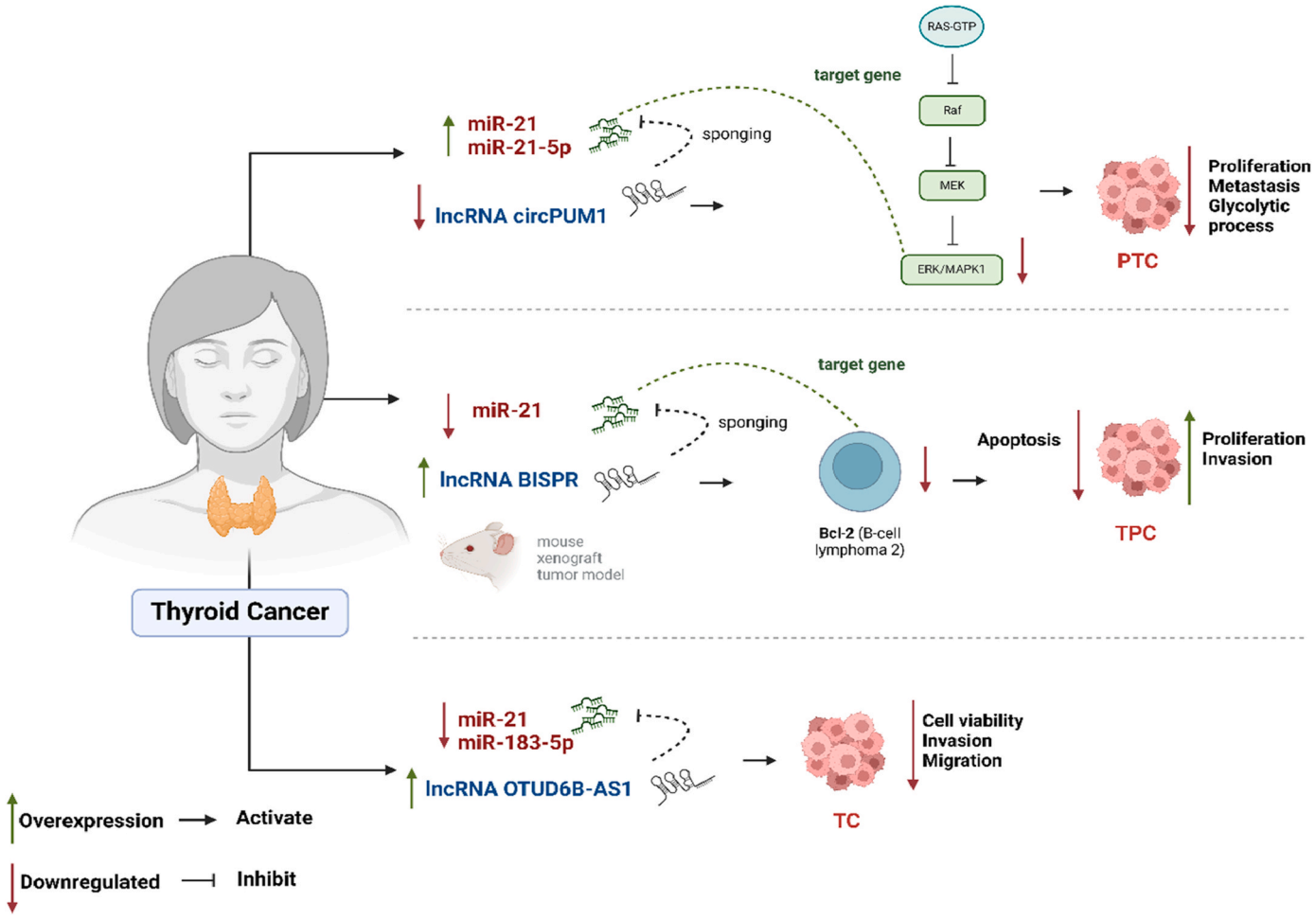

Fig. 9. The figure displays the effect of miR-21 up and downregulation on thyroid cancer progression and metastasis.

expression levels. A ceRNA mechanism where IUR sponges miR-21 to modulate PTEN and affect ESCC cell proliferation and apoptosis was also suggested [164]. Indeed, IUR over-expression increased PTEN gene expression, whereas miR-21 overexpression showed the opposite effect; besides, both IUR and PTEN over-expression inhibited cell proliferation and promoted apoptosis, whereas miR-21 overexpression showed the opposite effect. Of note, IUR and miR-21 did not affect each other [164].

8.3. *Laryngeal squamous cell carcinoma*

Laryngeal squamous cell carcinoma (LSCC) is a frequent kind of head and neck cancer, which is responsible for 2.4% of new cancer cases and 2.1% of cancer-related fatalities [165,166]. LSCC primarily affects males over the age of 40 [167]. The frequency of LSCC is rising, and more young individuals are now suffering from this condition. Early-stage LSCC may be treated with surgery, chemotherapy, radiation, or a combination of these treatments [168]. However, even after receiving active treatment, patients with advanced LSCC have a poor prognosis. Novel therapeutic strategies are therefore required, although the uncertain LSCC pathophysiology makes it challenging to create them [169].

8.3.1. *GAS5 lncRNA*

Regarding the role of lncRNA-miR-21 interplay in LSCC, the miR143HG-miR-21, and the GAS5-miR-21 associations have been reported [170,171]. Both lncRNAs, miR143HG and GAS5, act as tumor suppressors in LSCC, where they are downregulated and inversely correlated with miR-21 [170,171]. Tissue samples from 62 LSCC patients (44 males, 18 females) were used to measure miR143HG and miR-21 expression levels by qPCR and methylation-specific-PCR. Results demonstrated that miR143HG's low expression levels are correlated with poor survival, and its overexpression increases miR-21 methylation [170]. In LSCC cells, miR143HG overexpression decreases miR-21 expression levels and inhibits cell migration and invasion. The opposite was instead observed with miR-21 overexpression [170]. To investigate the GAS5-miR-21 interplay, a total of 59 tissue samples from LSCC patients, along with the LSCC cell lines SUN1076 and SNU899, were used [171]. As mentioned above, qPCR results indicated that GAS5 is downregulated in LSCC tissues and cells, and its expression levels are correlated with LSCC patients' clinicopathological traits [171]. GAS5 overexpression suppresses cell proliferation and enhances cell apoptosis; besides, the apoptosis regulator, BCL2 associated x (BAX), and the cell-cycle progression promoter, cyclin-dependent kinase (CDK6), which are also miR-21 target genes, resulted increased and decreased respectively both at gene and protein level. Of note, miR-21 overexpression reversed all these effects [171].

9. Thyroid cancer

Thyroid cancer (TC) forms in the thyroid gland, a small butterfly-shaped gland at the base of the neck. This gland produces hormones that regulate metabolism and help to control body temperature, blood pressure, and heart rate [172]. Thyroid papillary carcinomas (TPC) are the most common thyroid cancers, with a prevalence of more than 80% [173,174]. Papillary carcinoma frequently involves a benign tumor with a good prognosis and effective treatment [173,174]. After thorough treatment, which typically includes thyroidectomy, radioactive iodine

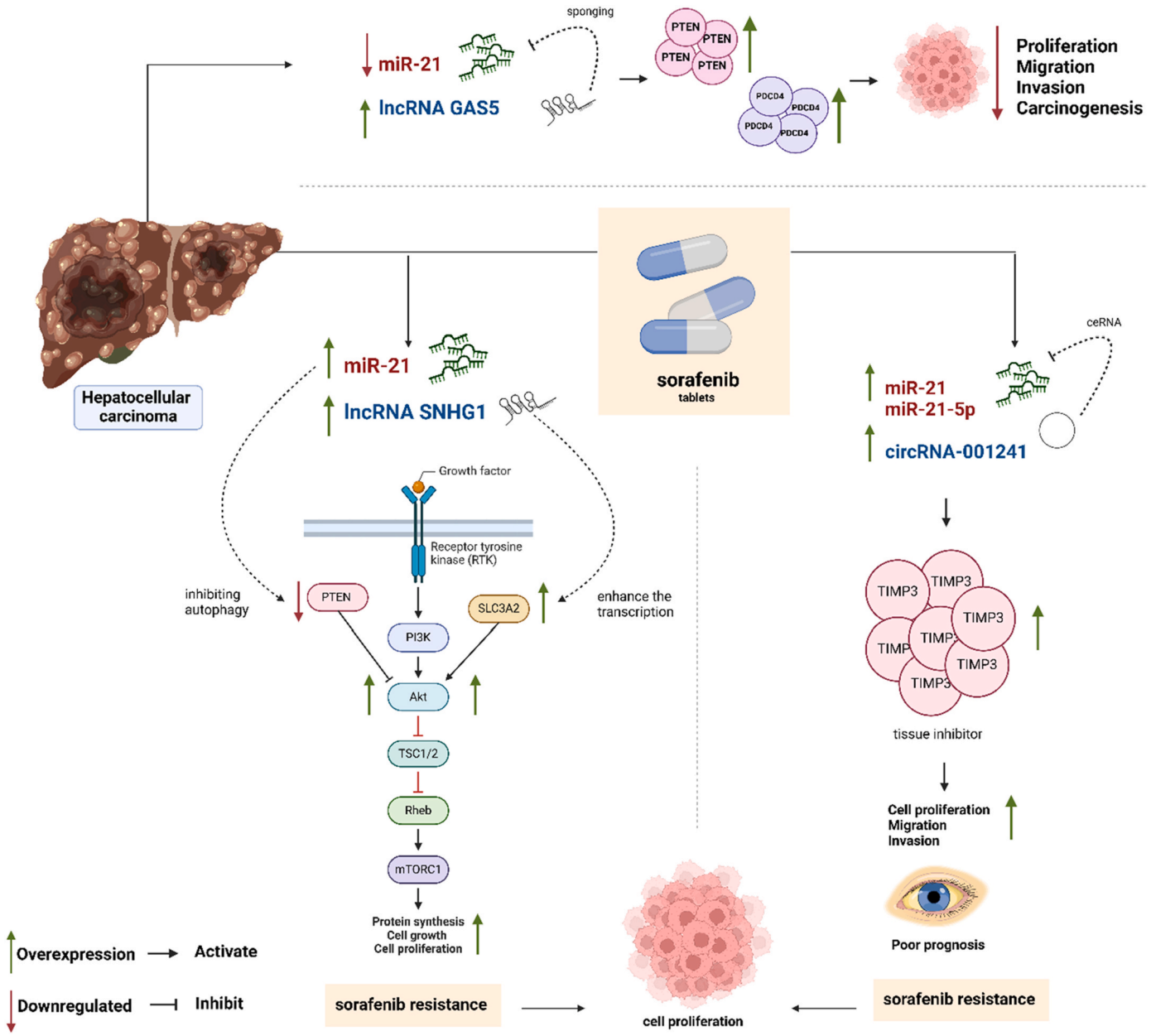

Fig. 10. The figure depicts the effects and molecular mechanisms of different miR-21-lncRNA axes in modulating Hepatocellular carcinoma progression and metastasis.

therapy (RAI), and thyroid-stimulating hormone (TSH) suppression therapy, the 5-year survival rate is over 90%. Nevertheless, TPC metastasis can cause a significant recurrence rate; therefore, investigating the molecular processes that underlie TPC is crucial [173,174]. The regulatory action of circRNAs also became crucial in PTC progression. Is this the case of the oncogenic circRNA called Circ-Pumilio 1 (circPUM1), whose expression resulted increased in both PTC tissues and cells. On the other hand, circPUM1 knockdown results in the suppression of cell proliferation, metastasis, and glycolytic processes in PTC cells [175]. Additionally, the anti-cancer impact of circPUM1 knockdown on PTC was also linked to the miR-21-5p/MAPK1 axis. The mitogen-activated protein kinase 1 (MAPK1) is a target gene of miR-21-5p, and circPUM1competes with miR-21-5p for the binding to MAPK1. Therefore, circPUM1 knockdown downregulates MAPK1 by upregulating miR-21-5p (Fig. 9) [175]. The biological function of BST2 interferon-stimulated positive regulator (BISPR), already known for promoting tumorigenesis in renal cell carcinoma [176] and oral cavity cancer [177], has been recently elucidated in TPC, as well as its relationship with miR-21-5p [178]. Microarray results showed that BISPR is highly expressed in TPC tissues compared to adjacent tissues, with lower expression levels. Moreover, low expression of BISPR in patients with TPC resulted positively correlated with higher survival time compared with patients with high BISPR expression [178]. Accordingly, BISPR knockdown counteracted TPC cell propagation and invasiveness and promoted apoptosis. In silico analysis, followed by dual luciferase reporter assay and RNA pull-down assay, indicated that miR-21-5p directly targets BISPR. Besides, BISPR prevents TPC cell proliferation and invasion by inhibiting miR-21-5p expression [178]. A further target of miR-21-5p is the anti-apoptotic gene B-cell lymphoma-2 (Bcl-2); in this respect, both miR-21-5p and BISPR knockdown suppressed Bcl-2 mRNA and protein expression. Collectively, results clarify the BISPR role in TPC development, as well as its relationship with miR-21-5p and the downstream target Bcl-2 (Fig. 9) [178]. Thyroid cancer growth and metastasis resulted strongly correlated with the expression of the

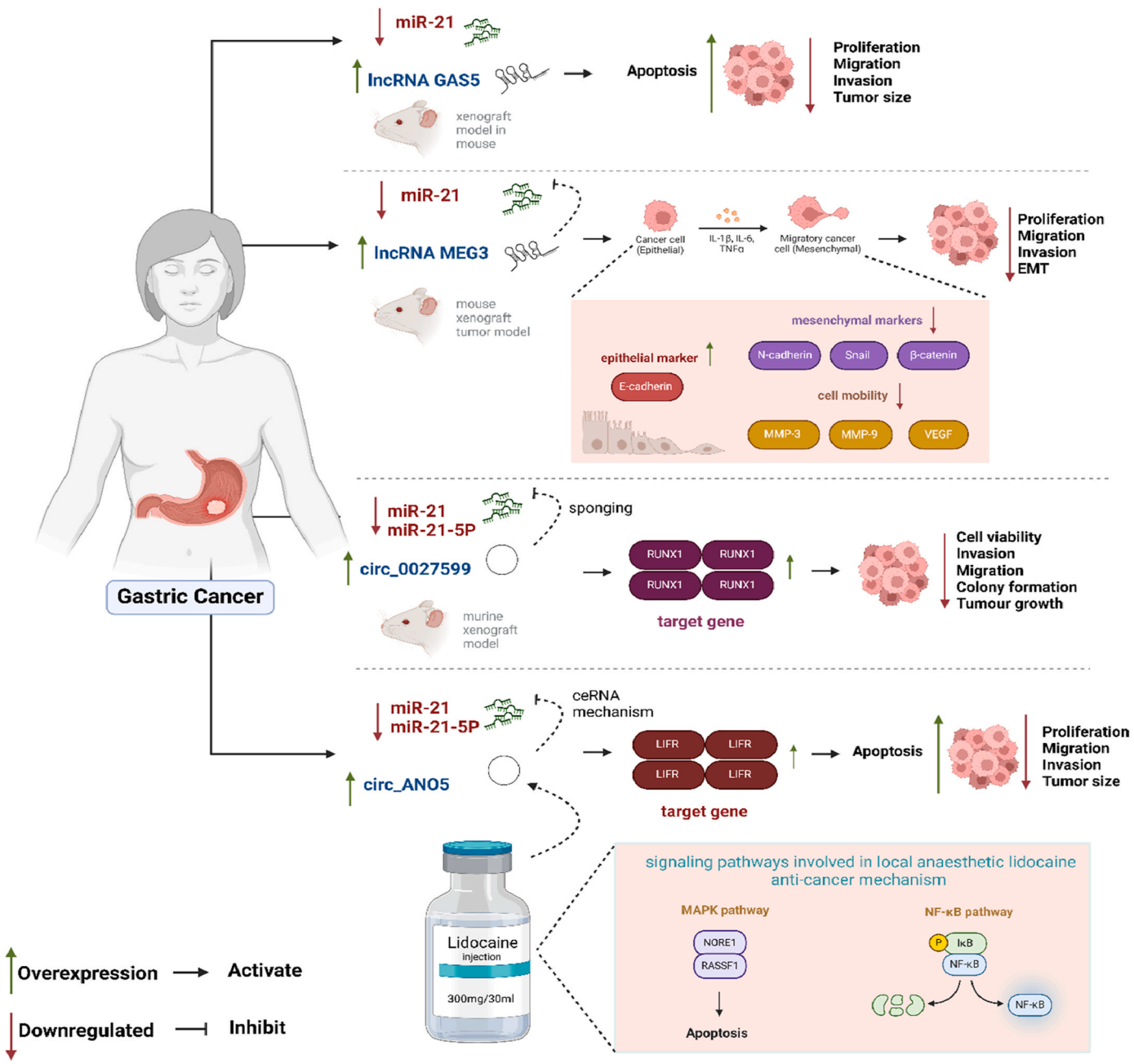

Fig. 11. The figure depicts the effects and molecular mechanisms of different miR-21-lncRNA axes in modulating gastric cancer progression and metastasis.

lncRNA OTUD6B antisense RNA 1 (OTUD6B-AS1) [179]. According to Wang et al. (2020), OTUD6B-AS1 functions as a tumor suppressor in TC, and its overexpression inhibits TC cell viability, migration, and invasion [179]. MiR-21 and miR-183-5p are both correlated with OTUD6B-AS1 activity, and their overexpression compromises the suppressive action of OTUD6B-AS1 on TC cell proliferation and invasiveness (Fig. 9) [179].

10. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is one of the fastest-growing malignancies with the highest rates of cancer-related mortalities worldwide. It is notably manifested in viral hepatitis but also in patients affected by chronic Hepatitis B and C with advanced fibrosis [180]. HCC incidence is higher in male individuals and in African and Asian populations where viral hepatitis is endemic [181]. If diagnosed early, HCC can be cured by surgical approaches or liver transplant; however, in most cases, HCC is diagnosed at later stages where severe obstructive symptoms, liver impairment, and a high rate of intrahepatic and extrahepatic metastasis are evident [182]. LncRNAs and miRNAs dysregulation have been associated with HCC cell metastasis, highlighting thus the potential of these epigenetic factors as novel HCC therapeutic targets [183,184].

10.1. GAS5 lncRNA

Several studies have demonstrated the significant role of lncRNAs/miR-21 regulatory interaction in HCC. According to Hu L et al., the lncRNA GAS5 acts as a tumor suppressor gene in HCC by downregulating miR-21 and its downstream targets [185]. Indeed, GAS5 and miR-21 expression in HCC tissues resulted lower and higher, respectively, compared to the adjacent normal liver tissues. Notably, GAS5 and miR-21 expression levels were also correlated with clinicopathological

parameters such as tumor size and TNM Classification of Malignant Tumors (TNM) stage [185]. Furthermore, the highly aggressive HCC cell line, HCCLM3, displayed the lowest level of GAS5 compared to the moderately and weakly aggressive cells, SMMC-7721 and Bel-7402, respectively [185]. Regarding the regulatory mechanism played by GAS5, the authors suggested that it may serve as a miR-21 sponge, hence sequestering miR-21 oncogenic function and affecting the expression of miR-21 targets, such as PDCD4 and PTEN. These targets play a key role in cancer cell migration and invasion and resulted downregulated in HCC tissues [185–187]. Previous studies reported a significant role of GAS5 in carcinogenesis and tumor progression, its prognostic value in various types of cancer [188], as well as the positive correlation between miR-21 overexpression and poor prognosis in HCC [189]. In this regard, a study by Hu L et al. (2016) provided further evidence of GAS5 and miR-21 prognostic value in HCC since GAS5 downregulation and subsequent miR-21 overexpression were also associated with low survival rates in HCC patients (Fig. 10) [185].

10.2. Other lncRNAs

A recent study demonstrates the implication of lncRNAs/miR-21 regulatory cross-talk in drug resistance in HCC patients [190,191]. The multi-kinase inhibitor sorafenib is one the first-line treatment for advanced HCC patients. by targeting the serine/threonine protein kinases Raf-1, B-Raf, as well as the vascular endothelial growth factor receptors (VEGFRs), and the platelet-derived growth factor receptor β (PDGFR-β), sorafenib showed to inhibit tumor growth, tumor-angiogenesis and induce apoptosis in a broad range of cancer cells [192]. However, the acquired resistance to sorafenib negatively reduces its effectiveness and anti-cancer properties [193]. Emerging studies demonstrated that Akt overexpression contributes to the acquired resistance to sorafenib and that the inhibition of this pathway reverses the acquired resistance by switching autophagy from a protective to a death-promoting role in HCC [194]. In this regard, miR-21 plays a key role in the acquired resistance of sorafenib by inhibiting autophagy through the Akt/PTEN pathway; indeed, sorafenib-resistant HCC (SR-HCC) cells showed increased miR-21 expression, decreased PTEN expression and Akt activation [195]. Tumor progression associated with Akt activation is also promoted by the lncRNA small nucleolar RNA host gene 1 (SNHG1), which is highly expressed in different types of cancer and promotes tumor growth and progression by regulating transcription of both local and distal genes [196–198]. In particular, SNHG1 was shown to enhance the transcription of the nearby gene solute carrier family 3 member 2 (SLC3A2) to activate the PI3K/AKT pathway [197]. A novel regulatory lncRNA-miRNA mechanism, different from the lncRNA-mediated sponge regulatory network, which involves both SNHG1 and miR-21 in sorafenib resistance via Akt pathway activation, has recently been reported in HCC cells. Specifically, sorafenib facilitates miR-21 translocation into the nucleus of HCC cells, where it promotes the expression of SNHG1. Then, SNHG1 contributes to sorafenib resistance by increasing SLC3A2 expression that, in turn, activates the Akt pathway (Fig. 10) [191].

A further regulatory axis, circRNA-001241/miR-21, has recently been proposed in mediating sorafenib resistance in HCC patients [190]. Circ-001241, which was found to significantly upregulated in HCC tissues and cells by acting as ceRNA, mediated HCC sorafenib-resistance by sponging miR-21-5p and increasing the expression of the tissue inhibitor of metalloproteinase 3 (TIMP3) (), a modulator of cell proliferation, migration, and invasion [190,199]. Conversely, the knockdown of circ-001241 significantly suppressed HCC cell proliferation and enhanced the sorafenib sensitivity. The enhanced expression of circ-00124 resulted also correlated with increased tumor size and poor prognosis, highlighting the clinical potential of the miR-21-5p/TIMP3 axis as an index of HCC patients' pathological stage (Fig. 10) [190].

11. Gastric cancer

Gastric cancer (GC) is one of the most common gastrointestinal malignant cancers worldwide. GC is more prevalent in males, and Eastern Asia countries have the highest reported incidence [200]. Additionally, the majority of cases are linked to bacterial or viral infections, such as *Helicobacter pylori* (*H. pylori*) or Epstein-Barr virus (EBV) [201,202]. Currently, there is no cure or a golden standard treatment strategy for GC, and the treatment options mainly depend on the disease stage. Treatments primarily aim to relieve symptoms rather than cure the disease [203,204]. Therefore, understanding the underlying carcinogenic mechanisms is needed for both early detection and setting targeted molecular therapeutic strategies.

11.1. GAS5 lncRNA

The involvement of lncRNAs/miR-21 regulatory interaction in GC occurrence and progression has been recently reported. In this regard, the association of GAS5 and miR-21 has been investigated both *in vivo* and *in vitro* [205]. Specifically, GAS5 expression resulted significantly downregulated in GC tissues and cells, whereas miR-21 expression was significantly increased. Moreover, overexpression of GAS5 inhibits proliferation, migration, and invasion of GC cells while promoting GC cell apoptosis [205]. MiR-21 has an oncogenic effect instead, and based on both in silico prediction and luciferase reporter assay, it is a target of GAS5. Indeed, overexpression of GAS5 in GC cells and xenograft mouse models led to a significant reduction of miR-21 expression, as well as the inhibition of GC cell tumorigenic ability and a decrease in tumor size (Fig. 11) [205].

11.2. MEG3 lncRNA

Another lncRNA acting as a tumor suppressor in GC is MEG3 [188]. Regarding the relationship between MEG3 and miR-21, a recent study demonstrated that MEG3 is downregulated in GC cells and tissues, whereas miR-21 is upregulated [206]. Besides, experiments *in vivo* using a mouse xenograft tumor model showed that MEG3 negatively regulates miR-21; indeed, MEG3 overexpression suppresses tumor growth and metastasis, whereas miR-21 overexpression has opposite effects and promotes metastasis [206]. Interestingly, the MEG3/miR-21 axis modulates GC cell mobility through EMT inhibition, a physio-pathological process where epithelial cells lose their typical features and acquire mesenchymal characteristics [206,207]. EMT plays a key role in malignancy since it increases tumor invasiveness and metastatic activity [207]. In particular, MEG3 overexpression was shown to inhibit EMT by increasing the epithelial marker E-cadherin and decreasing the mesenchymal markers, N-cadherin, Snail, and β-catenin. Besides, MEG3 overexpression suppressed gastric cancer cell mobility by downregulating the matrix metalloproteinases (MMPs), MMP-3 and MMP-9, and the vascular endothelial growth factor (VEGF) [206]. MMP-3 and MMP-9 are enzymes involved in t extracellular matrix (ECM) degradation to promote cell invasion, whereas VEGF promotes endothelial cell proliferation, migration and invasion [206]. Therefore, the MEG3/miR-21 axis participates in GC cell invasiveness and metastatic capability through EMT regulation.

11.3. Other lncRNAs

Given GC invasiveness and recurrent nature, there has been growing interest in assessing the competitive inhibition of oncogenic miRNAs activity by utilizing the sponging mechanism of circRNA (Fig. 11) [208,209]. CircRNA is indeed an efficient miRNA sponge, mainly due to its higher resistance to nuclease degradation compared to its linear counterpart RNA [210]. In this regard, a recent study demonstrated that synthetic circRNA sponges are a valuable strategy for a targeted loss-of-function of specific miRNAs, both *in vivo* and *in vitro*. In

particular, an artificial circRNA was demonstrated to inhibit GC cell proliferation through sequestering miR-21 oncogenic functions; miR-21 suppression promoted, in turn, the upregulation of downstream gene targets such as DAXX, a key tumor suppressor gene [208]. Han J et al. (2016) reported that circ_0027599 upregulated the expression of runt-related transcription factor 1 (RUNX1) in GC cells through sponging miR-21-5p [211]. Both circ_0027599 and RUNX1 () are downregulated in GC. Accordingly, either circ_0027599 or RUNX1 overexpression repressed the malignant behavior of GC cells by inhibiting their viability, invasion, migration, and colony formation. Besides, circ_0027599 overexpression repressed tumor growth in a murine xenograft model. On the other hand, RUNX1 knockdown reverted the effect of circ_0027599 overexpression on GC cell behavior, suggesting circ_0027599 positively regulates RUNX1 expression. Further investigations on the relationship between circ_0027599, miR-21-5p, and RUNX1 suggested that RUNX1 is a direct target of miR-21-5p, and circ_0027599, positively regulates RUNX1 expression acting as a sponge for miR-21-5p (Fig. 11) [211]. A further lncRNAs/miR-21 axis involved in GC progression engages circ_ANO5, miR-21 and its target gene leukemia inhibitory factor receptor (LIFR), known for anticancer properties in different cancers, including pancreatic cancer, hepatocellular carcinoma [212,213]. Interestingly, the circ_ANO5/miR-21-5p/LIFR axis was implicated in the anti-tumor molecular mechanism of the local anesthetic lidocaine [212]. Several studies highlighted the benefits of lidocaine in cancer treatment, including GC. Indeed, lidocaine was shown to promote apoptosis and inhibit proliferation and malignant behavior of GC cells through several signaling pathways, including MAPK and NF-κB [214–216]. Concerning the above-mentioned axis, lidocaine promoted circ_ANO5 upregulation and miR-21-5p downregulation, resulting in a decrease in GC cell viability migration and invasion. This effect was instead reversed with either miR-21-5p overexpression or circ_ANO5 depletion [212]. Moreover, a ceRNA mechanism was also proposed where circ_ANO5 sponges miR-21-5p counteract its oncogenic functions and allow the expression of its target gene LIFR (Fig. 11) [212].

12. Other cancers

12.1. GAS5 lncRNA

The GAS5-miR-21 interaction is one of the most accounted for having a high impact on cancer growth and progression; indeed, as previously described, this axis plays a crucial role in OC, CRC, NSCLC, OSCC, LSCC, HCC, and GC regulation. In addition, a possible role of GAS5 and miR-21 has also been described in bladder cancer and osteosarcoma (OS) lung metastasis [217,218]. In bladder cancer, GAS5 targets miR-21 to regulate PTEN and affect cell proliferation and apoptosis; besides, high levels of GAS5 (and low levels of miR-21) in bladder cancer patients are associated with relatively longer survival rates [217]. In patients with OS, a common primary bone malignancy that typically affects adolescents [219], GAS5 is downregulated (while miR-21 is upregulated) compared to healthy controls [218]. Lungs are considered one of the most common sites for OS metastasis [220,221]; in this regard, GAS expression levels in OS patients with lung metastasis are even lower than in patients without metastasis (while miR-21 expression levels are even higher), suggesting a correlation between GAS5 (and miR-21) expression levels and the disease severity [218]. Furthermore, GAS5 downregulation also enhances migration and invasion of OS cells promoting EMT, as indicated by the decrease (at gene and protein level) of the epithelial marker E-cadherin and the increase of mesenchymal marker vimentin [218].

12.2. CASC2 lncRNA

Similarly to what is described in CC [65], the CASC2/miR-21/PTEN regulatory axis can also modulate pancreatic cancer development and progression [222]. CASC2 resulted indeed downregulated in different pancreatic cancer cell lines (CAPAN-1, BxPC-3, JF305, PANC-1, and SW1990) compared with normal human pancreatic HPDE6-C7 cells [222]. Besides, CACS2 was shown to inhibit cell migration and invasion by targeting miR-21, ultimately leading to the decrease of the miR-21 target gene, PTEN (as demonstrated by qRT-PCR and Western blot analysis) [222]. It is important to mention that a high global burden, poor prognosis and inadequate therapeutic interventions characterize pancreatic cancer [223]. These findings suggest the relevance of the novel regulatory CASC2/miR-21/PTEN axis in pancreatic cancer development, which might pave the way for a new therapeutic or prognostic approach.

12.3. MEG3 lncRNA

Wu et al. (2020) found that the lncRNA MEG3 can inhibit tumor growth, tumor metastasis, and melanoma formation by modulating the miR-21/E-cadherin axis [224]. Melanoma is one of the most aggressive forms of cutaneous cancer arising from the melanocytes [225]. Localized melanoma can be surgically removed, ensuring the best prognosis. On the other hand, when undiagnosed or misdiagnosed, melanoma aggressively metastasizes and presents a poor prognosis [225,226]. Therefore, accurate diagnostic biomarkers are urgently needed to improve the overall survival rates in melanoma patients. In this regard, it was reported that MEG3 and E-cadherin mRNA and protein expression levels are positively correlated in melanoma cell lines; besides, a positive correlation regarding their functionality also exists since both MEG3 and E-cadherin suppress melanoma formation and growth and metastasis [224]. In fact, MEG3 upregulation inhibits melanoma formation, whereas E-cadherin knockdown increases melanoma metastasis and progression, overall confirming MEG3 tumor suppressor functions. Dual luciferase assay suggested that miR-21 is a downstream target of MEG3, and E-cadherin is a downstream target of miR-21 [224].

12.4. Other lncRNAs

The lncRNA X-inactive specific transcript (XIST) is also downregulated in OS tissues and cells, and it is associated with OS recurrence and patients' low survival [227]. Lentivirus-mediated overexpression of XIST in osteosarcoma cells and a xenograft mouse model suggested a tumor suppressor role of this lncRNA; indeed, XIST inhibits OS formation and progression and suppresses the EMT process [227]. This inhibitory effect is associated with a ceRNA mechanism, where XIST competitively binds miR-21-5p to increase the expression of programmed cell death 4 (PDCD4), a tumor suppressor frequently down-regulated in various types of cancer [227,228]. The XIST/miR-21-5p/PDCD4 axis may thus represent a potential biomarker or therapeutic target for OS [227]. Finally, a potential prognostic marker and therapeutic target in prostate cancer (PC) is the circSLC8A1/miR-21 axis. Functional *in vitro* analysis using PC cells demonstrated that this axis can modulate cell proliferation and migration [229]. Besides, gene ontology (GO) enrichment analysis showed that the circSLC8A1/miR-21 axis is involved in regulating cell proliferation, migration, angiogenesis, and EMT, while KEGG pathway analysis showed that the circSLC8A1/miR-21 axis is related to the MAPK signaling pathway [229].

13. Conclusion

In recent years, there has been an increasing recognition of the potential diagnostic and therapeutic applications of ncRNA molecules. The advancements in high-throughput sequencing technologies and machine learning algorithms have facilitated the discovery of novel ncRNAs and their cellular roles, as well as novel lncRNA-miRNA regulatory axes with potential prognostic and diagnostic value in various human pathological conditions, including cancer. The article delves into the recent discoveries regarding the roles and pathophysiological implications of the

Table 1
Signaling pathways relevant to Mir-21, functional implications, and role of lncRNA in various types of cancer.

lncRNA	Type of Cancer	Target gene/Signalling Pathways regulated	Role of lncRNA	Functional Implications	References
BISPR	Thyroid papillary carcinoma (TPC)		Oncogenic	↑ development and progression of TPC	[232]
BRE-AS1	Breast cancer	↑ PTEN expression	Tumor suppressor	↓ cell proliferation, migration, invasion	[56]
CASC2	Pancreatic carcinoma	PTEN/Akt	Tumor suppressor	↓ cancer migration and invasion	[222]
	Non-small cell lung cancer (NSCLC)	PTEN/PI3K/Akt	Tumor suppressor	↑ inhibitory effect of cisplatin on cell viability	[233,234]
	Lung adenocarcinoma (LUAD)	CASC2/miR-21/p53 axis; ↓ miR-21 expression and ↑ p53 expression	Tumor suppressor	↓ cell proliferation and ↑ apoptosis	[233,234]
	Colorectal cancer (CRC)		Tumor suppressor	↓ advanced tumor node metastasis stage and tumor size	[95]
	Cervical cancer	↑ PTEN expression and ↓ p-AKT protein	Tumor suppressor	↑ sensitization of cervical cancer to cisplatin (DDP) and ↓ cancer cell proliferation, advanced tumor-node-metastasis stage and tumor size	[65]
	Glioma	↓ miR-21 expression	Tumor suppressor	↓ tumor size, cell proliferation, migration, invasion and ↑ apoptosis	[139,235]
CASC7	Breast cancer	miR-21-5p/FASLG axis	Tumor suppressor	↓ advancement of breast cancer, cell proliferation, migration, and invasion	[54]
Circ_ANO5	Gastric cancer	Circ_ANO5/miR-21-5p/LIFR axis	Tumor suppressor	↓ cell proliferation, migration, invasion, tumor growth *in vivo* and ↑ apoptosis	[236]
Circ-21	Breast cancer	↑ PARP-1 and ↓ VEGF expression	Tumor suppressor	↑ drug efficacy and the antitumor activity of doxorubicin and ↓ tumor cell proliferation	[55]
circACAP2	Colorectal cancer (CRC)	circRNA-ACAP2/hsa-miR-21-5p/ Tiam1 regulatory feedback circuit; ↓ Tiam1 expression	Oncogenic	↑ cell proliferation, migration, and invasion	[98]
circEPB41L2	Colorectal cancer (CRC)	PTEN/AKT signaling pathway	Tumor suppressor	↓ cell proliferation, migration, invasion and ↑ apoptosis	[90]
circPUM1	Thyroid papillary carcinoma (TPC)	miR-21-5p/MAPK1 axis	Oncogenic	↑ cell growth, metastasis, and glycolytic processes.	[237]
CircRNA_0027599	Gastric cancer	miR-21-5p/RUNX1 axis	Tumor suppressor	↓ cell viability, colony formation, migration, invasion, cell cycle process *in vitro* and tumor growth *in vivo*	[238]
CircRNA-001241	Hepatocellular carcinoma (HCC)	miR-21-5p/TIMP3 axis; ↓ miR-21-5p and ↑ TIMP3 expression	Tumor suppressor	↓ sorafenib-resistance and cell proliferation	[239]
CircSLC8A1	Prostate Cancer	circSLC8A1/miR-21 axis	Tumor suppressor	↓ angiogenesis, cell proliferation and migration	[229]
DGCR5	Colorectal cancer (CRC)		Tumor suppressor	↓ progression in clinical stages and cancer cell proliferation *in vitro*	[94]
	Glioma	miR-21/Smad7 and miR-23a/PTEN axis	Tumor suppressor	↓ cell proliferation, migration, invasion and ↑ apoptosis	[136]
GAS5	Hepatocellular carcinoma		Tumor suppressor	↓ tumor size, TNM stage, cancer migration and invasion	[185]
	Gastric cancer		Tumor suppressor	↓ tumorigenic ability and tumor size	[205]
	Lung Metastasis of Osteosarcomas	↑ E-cadherin and ↓ vimentin, ZEB1, and ZEB2	Tumor suppressor	↓ EMT and cancer migration and invasion	[218]
	Bladder cancer		Tumor suppressor	↑ antiproliferative and proapoptotic effects	[217]
	Non-small cell lung cancer (NSCLC)	NBAT1/miR-21/SOX7 axis	Tumor suppressor	↑ IR-induced cell apoptosis of A549 cells	[240,241]
	Colorectal cancer (CRC)	miR-21/LIFR axis	Tumor suppressor	↓ tumor growth, metastasis and invasion	[82]
	Oral squamous cell carcinoma (OSCC)	miR-21/PTEN axis	Tumor suppressor	↓ EMT, cancer proliferation, migration and invasion	[156]
	Ovarian cancer	GAS5/miR-21/SPRY2 signaling pathway; ↓ miR-21 and ↑ SPRY2 expression	Tumor suppressor	↓ advanced clinical stage	[80]
	Laryngeal Squamous Cell Carcinoma (LSCC)	↑ BAX mRNA expression (apoptosis) and ↓ CDK6 mRNA expression (proliferation)	Tumor suppressor	↓ cell proliferation and ↑ apoptosis	[171]
HLA-F-AS1	Ovarian cancer	miR-21-3p/PEG3 axis	Tumor suppressor	↓ cancer development *in vivo* and *in vitro*	[81]
IUR	Esophageal squamous cell carcinoma	↑ PTEN expression	Tumor suppressor	↓ cell proliferation and ↑ apoptosis	[242]
LINC00312	Colorectal cancer (CRC)	LINC00312/miR-21/PTEN axis	Tumor suppressor	↓ cancer proliferation and metastasis	[93]
	Acute Myeloid Leukemia (AML)	miR-21/PTEN axis	Tumor suppressor	↓ proliferation rate of AML cells	[101]
LINC00968	Lung adenocarcinoma	miR-21-5p/SMAD7 axis	Tumor suppressor	↓ cancer progression, disease relapse, and recurrence rates	[243]
LOC100507144	Colorectal cancer (CRC)	CD44/Nanog/Sox2/miR-302/miR-21 axis	Oncogenic	↑ EMT, cancer progression, migration and metastasis	[96]

(*continued on next page*)

Table 1 (*continued*)

lncRNA	Type of Cancer	Target gene/Signalling Pathways regulated	Role of lncRNA	Functional Implications	References
LOXL1-AS1	Cervical squamous cell carcinoma (CSCC)	↓ miR-21 and ↑ RHOB expression	Tumor suppressor	↓ cell invasion and migration	[68]
MALAT1	Colorectal cancer (CRC)		Oncogenic	↑ cell invasion, migration ability, and tumor formation	[97]
MEG3	Gastric cancer	MEG3/miR-21 axis	Tumor suppressor	↓ EMT, cell mobility, tumor growth and metastasis	[206]
	Melanoma	miR-21/E-cadherin axis; ↓ miR-21 and ↑ E-cadherin expression	Tumor suppressor	↓ tumor growth, tumor metastasis and formation	[224]
	Non-small cell lung cancer (NSCLC)	miR-21-5p/PTEN axis; ↑ PTEN expression (involved in PI3K/AKT signaling pathway) miR-21-5p/SOX7 axis; ↑ SOX7 expression	Tumor suppressor	↓ cell migration and invasion and ↑ cisplatin sensitivity	[244,245]
	Breast cancer	PI3K/Akt pathway	Tumor suppressor	↓ tumorigenesis and progression in the clinical stage	[63]
	Cervical cancer	MEG3/miR-21/PTEN axis	Tumor suppressor	↓ tumor grade and metastasis	[66,67]
	Chronic Myeloid Leukemia (CML)		Tumor suppressor	↓ imatinib resistance, cell proliferation and ↑ cell apoptosis	[104]
	Glioma		Tumor suppressor	↓ cell proliferation, migration, and invasion	[246]
	Oral squamous cell carcinoma (OSCC)		Tumor suppressor	↓ cell proliferation and migration	[157]
miR143HG	Laryngeal squamous cell carcinoma		Tumor suppressor	↓ rate of cell migration, invasion and ↑ methylation of miR-21	[247]
NBAT1	Endometrial cancer	↑ PTEN expression	Tumor suppressor	↓ cell proliferation, migration, invasion and ↑ apoptosis	[78]
	Glioma	NBAT1/miR-21/SOX7 axis; ↑ SOX7 expression	Tumor suppressor	↓ cell proliferation, migration, and invasion, progression and metastasis	[134]
OTUD6B-AS1	Thyroid cancer		Tumor suppressor	↓ tumor size, clinical stage, lymphatic metastasis, cell viability, migration and invasion	[248]
	Colorectal cancer (CRC)	OTUD6B-AS1/miR-21-5p/PNRC2 axis; ↑ PNRC2 expression	Tumor suppressor	↓ EMT, cell proliferation, migration, invasion and ↑ cell apoptosis	[249]
PLAC2	Non-small cell lung cancer (NSCLC)		Tumor suppressor	↓ cancer cell migration and invasion	[250]
RUNX1-1T1	Endometrial cancer	↓ mature miR-21 expression	Tumor suppressor	↓ the maturation process of miR-21 and cell proliferation	[77]
SNHG1	Hepatocellular carcinoma	Akt pathway	Oncogenic	↑ sorafenib resistance and ↓ its ability to induce apoptosis and autophagy	[191]
SNHG9	Non-small cell lung cancer (NSCLC)		Tumor suppressor	↓ cell proliferation and cancer progression	[251]
TCL6	Retinoblastoma cancer	PTEN/PI3K/AKT signaling pathway involved in TCL6/miR-21 axis; ↑ PTEN expression	Tumor suppressor	↓ cell proliferation and ↑ apoptosis	[252]
WDFY3-AS2	Kidney renal clear cell carcinoma (KIRC)	WDFY3-AS2/TIMP3 pathway	Tumor suppressor	↓ tumor grade, size, lymph node metastasis, distant metastasis, and TNM stage	[253]
XIST	Osteosarcoma (OS)	XIST/miR-21-5p/PDCD4 axis; ↑ PDCD4 expression	Tumor suppressor	↓ EMT, cell invasion and migration	[227]

miR-21-lncRNA regulatory axis in cancer onset and development. The data collected suggests that specific lncRNAs such as MEG3, CASC2, and GAS5 are strongly associated with miR-21 in various types of cancer, including gastric, cervical, lung, and glioma. These lncRNAs are well-known for their ability to suppress tumors and are commonly down-regulated in different types of tumors. On the other hand, their over-expression has been linked with preventing tumor formation and development by modulating various mechanisms and oncogenic signaling pathways. Our work emphasizes the significance of these regulatory pathways in cancer and their potential for use in cancer therapy as diagnostic and prognostic markers. Indeed, due to their stability in serum and other body fluids, non-invasive detection, and tissue-specific expression patterns, NcRNAs represent promising and robust diagnostic biomarkers [230,231]. For instance, lncRNA resistance to ribonuclease degradation makes them a suitable candidate for detection in various biological samples and body fluids, including blood, urine, and tissue biopsies [230]. Most importantly, the specificity and dysregulation of lncRNAs expression in different human cancers provides a unique opportunity for the development of highly specific therapeutic biomarkers. Therefore, elucidating novel miR-21-lncRNA regulatory axis in cancer may play an essential role in grasping cancer pathophysiology and could lead to innovative treatments for human cancer. While the complexity of miR-21-lncRNA regulatory cross-talk in cancer remains enigmatic, high-throughput sequencing technologies and functional genomics approaches promise further elucidation of their functional roles in cancer.

14. Future perspective

Although the mentioned studies present a major first step into understanding the complex regulatory cross-talk in cancer pathophysiology, the full extent of these regulatory networks remains to be determined. It is also worth noting that the existing studies on lncRNA have largely concentrated on their function as ceRNA or miRNA sponges. One area of interest is exploring other regulatory functions of lncRNA in cancer-related pathways. For example, investigating the role played by lncRNA in epigenetic modifications, primarily methylation and acetylation, could be an interesting approach to gaining helpful information in this field. Additionally, since most of the regulatory cross-talks investigated so far involve a binary correlation, an interesting future avenue could be the discovery of large interconnected networks. In this context, secondary indirect interactions may also uncover a profound complex regulatory network playing an essential role in cancer pathophysiology. Moreover, the molecular requirements for optimal

ceRNA activity remain largely obscure; indeed, those ceRNA networks are influenced by various factors, including the abundance of regulatory molecules, probable interplay with RBPs and RNA editing, which may significantly impact the cellular final fate [46].

The studies demonstrating the significance of the miR-21-lncRNA regulatory axis provide a valuable perspective in understanding the complex mechanistic pathways underlying human cancer. Nonetheless, it is worth mentioning that most studies investigating the miR-21-lncRNA regulatory axis and their interaction are based on in silico bioinformatics and machine learning algorithms miRNA predictions. Therefore, more *in vivo* and *in vitro* studies, as well as animal models, are needed to verify and validate these regulatory cross-talks and further highlight their clinical utility for understanding human cancer pathophysiology; indeed, it is also imperative that forthcoming studies delve into finding the best pre-clinical models to study human lncRNAs interactions. In addition, many of these studies used dual luciferase assays to confirm the downstream targets of lncRNAs and associated cancer-related signaling pathways, and only a few have investigated the expression levels with clinicopathological parameters such as tumor size and TNM stage. Therefore, the absence of clearly established and verified lncRNA tailored to particular types of cancer and stages presents a major hurdle in their practical application in a clinical setting. Thus, more functional studies are needed to elucidate the clinical relevance and validate the potential prognostic tool of these regulatory molecules.

In summary, these regulatory cross-talks point out the existence of novel and complex RNA networks in human cancer and suggest using these networks in cancer therapy and diagnosis (Table 1). Implementing miRNA and lncRNA-targeted therapies in clinical practice remains in its infancy; indeed, numerous obstacles of both a clinical and regulatory nature must be overcome before these therapies can become clinically relevant.

Ethics approval and consent to participate

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CRediT authorship contribution statement

Roberta Giordo: Writing – original draft, Conceptualization. **Fatemeh Abdullah M. Ahmadi:** Writing – original draft, Visualization. **Nedal Al Husaini:** Writing – original draft, Visualization. **Noora Rashid A.M. Al-Nuaimi:** Writing – original draft, Visualization. **Salma M.S. Ahmad:** Visualization, Writing – review & editing. **Gianfranco Pintus:** Writing – review & editing, Supervision, Conceptualization. **Hatem Zayed:** Writing – review & editing.

Declaration of competing interest

The authors declare they have no conflict of interest.

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References

[1] C. Richard Boland, Non-coding RNA: it’s not junk, Dig. Dis. Sci. 62 (5) (2017) 1107–1109.
[2] J.C. Venter, et al., The sequence of the human genome, Science 291 (5507) (2001) 1304–1351.
[3] A. Ahmad, Non-coding RNAs: a tale of junk turning into treasure, Non-coding RNA Research 1 (1) (2016) 1.
[4] A. Kapusta, C. Feschotte, Volatile evolution of long noncoding RNA repertoires: mechanisms and biological implications, Trends Genet.: TIG (Trends Genet.) 30 (10) (2014) 439–452.
[5] D.P. Bartel, MicroRNAs: genomics, biogenesis, mechanism, and function, Cell 116 (2) (2004) 281–297.
[6] D. Green, T. Dalmay, T. Chapman, Microguards and micromessengers of the genome, Heredity 116 (2) (2016) 125–134.
[7] S. Sekulovski, S. Trowitzsch, Transfer RNA processing - from a structural and disease perspective, Biol. Chem. 403 (8–9) (2022) 749–763.
[8] A.G. Seto, R.E. Kingston, N.C. Lau, The coming of age for Piwi proteins, Mol. Cell. 26 (5) (2007) 603–609.
[9] Y.W. Iwasaki, M.C. Siomi, H. Siomi, PIWI-interacting RNA: its biogenesis and functions, Annu. Rev. Biochem. 84 (2015) 405–433.
[10] F.P. Marchese, I. Raimondi, M. Huarte, The multidimensional mechanisms of long noncoding RNA function, Genome Biol. 18 (1) (2017) 206.
[11] L. Statello, et al., Gene regulation by long non-coding RNAs and its biological functions, Nat. Rev. Mol. Cell Biol. 22 (2) (2021) 96–118.
[12] N. Gao, et al., Long non-coding RNAs: the regulatory mechanisms, research strategies, and future directions in cancers, Front. Oncol. 10 (2020) 598817.
[13] Y. Fang, M.J. Fullwood, Roles, functions, and mechanisms of long non-coding RNAs in cancer, Dev. Reprod. Biol. 14 (1) (2016) 42–54.
[14] W.Y. Zhou, et al., Circular RNA: metabolism, functions and interactions with proteins, Mol. Cancer 19 (1) (2020) 172.
[15] W.-Y. Zhou, et al., Circular RNA: metabolism, functions and interactions with proteins, Mol. Cancer 19 (1) (2020) 172.
[16] Y. Ma, et al., A comprehensive overview of circRNAs: emerging biomarkers and potential therapeutics in gynecological cancers, Front. Cell Dev. Biol. 9 (2021) 709512.
[17] L.A. Macfarlane, P.R. Murphy, MicroRNA: biogenesis, function and role in cancer, Curr. Genom. 11 (7) (2010) 537–561.
[18] S.D. Hatfield, et al., Stem cell division is regulated by the microRNA pathway, Nature 435 (7044) (2005) 974–978.
[19] J.S. Mattick, I.V. Makunin, Small regulatory RNAs in mammals, Hum. Mol. Genet. 14 (Spec No 1) (2005) R121–R132.
[20] A.M. Posadino, et al., NADPH-derived ROS generation drives fibrosis and endothelial-to-mesenchymal transition in systemic sclerosis: potential cross talk with circulating miRNAs, Biomol. Concepts 13 (1) (2022) 11–24.
[21] R. Giordo, et al., EndMT regulation by small RNAs in diabetes-associated fibrotic conditions: potential link with oxidative stress, Front. Cell Dev. Biol. 9 (2021) 683594.
[22] N. Wehbe, et al., MicroRNAs in cardiac hypertrophy, Int. J. Mol. Sci. 20 (19) (2019) 4714.
[23] I. Floris, et al., Gestational diabetes mellitus impairs fetal endothelial cell functions through a mechanism involving microRNA-101 and histone methyltransferase enhancer of zester homolog-2, Arterioscler. Thromb. Vasc. Biol. 35 (3) (2015) 664–674.
[24] G. Spinetti, et al., MicroRNA-15a and microRNA-16 impair human circulating proangiogenic cell functions and are increased in the proangiogenic cells and serum of patients with critical limb ischemia, Circ. Res. 112 (2) (2013) 335–346.
[25] M. Gopikrishnan, et al., Therapeutic and diagnostic applications of exosomal circRNAs in breast cancer, Funct. Integr. Genom. 23 (2) (2023) 184.
[26] A.A. Abbas, et al., Implications and theragnostic potentials of circular RNAs in rheumatic diseases, Int. J. Biol. Macromol. (2023) 123783.
[27] H. Almaghrbi, et al., Non-coding RNAs as biomarkers of myocardial infarction, Clin. Chim. Acta (2023) 117222.
[28] H. Dehaini, et al., MicroRNAs as potential pharmaco-targets in ischemia-reperfusion injury compounded by diabetes, Cells 8 (2) (2019) 152.
[29] R. Giordo, et al., Metformin-mediated epigenetic modifications in diabetes and associated conditions: biological and clinical relevance, Biochem. Pharmacol. (2023) 115732.
[30] R. Giordo, et al., Disease-associated regulation of non-coding RNAs by resveratrol: molecular insights and therapeutic applications, Front. Cell Dev. Biol. 10 (2022) 894305.
[31] I. Ramli, et al., Effect of resveratrol on pregnancy, prenatal complications and pregnancy-associated structure alterations, Antioxidants 12 (2) (2023) 341.
[32] Y. Peng, C.M. Croce, The role of MicroRNAs in human cancer, Signal Transduct. Targeted Ther. 1 (2016) 15004.
[33] M. Bacci, et al., miR-155 drives metabolic reprogramming of ER+ breast cancer cells following long-term estrogen deprivation and predicts clinical response to aromatase inhibitors, Cancer Res. 76 (6) (2016) 1615–1626.
[34] M.L. Taddei, et al., Senescent stroma promotes prostate cancer progression: the role of miR-210, Mol. Oncol. 8 (8) (2014) 1729–1746.
[35] M. Hashemi, et al., Pre-clinical and clinical importance of miR-21 in human cancers: tumorigenesis, therapy response, delivery approaches and targeting agents, Pharmacol. Res. 187 (2023) 106568.
[36] A.-M. Aloizou, et al., The role of MiRNA-21 in gliomas: hope for a novel therapeutic intervention? Toxicol Rep 7 (2020) 1514–1530.
[37] T. Liu, et al., Diagnostic role of circulating MiR-21 in colorectal cancer: a update meta-analysis, Ann. Med. 53 (1) (2021) 87–102.
[38] S. Najjary, et al., Role of miR-21 as an authentic oncogene in mediating drug resistance in breast cancer, Gene 738 (2020) 144453.
[39] L. Qiu, G. Weng, The diagnostic value of serum miR-21 in patients with ovarian cancer: a systematic review and meta-analysis, J. Ovarian Res. 15 (1) (2022) 51.

[40] G. Du, D. Cao, L. Meng, miR-21 inhibitor suppresses cell proliferation and colony formation through regulating the PTEN/AKT pathway and improves paclitaxel sensitivity in cervical cancer cells, Mol. Med. Rep. 15 (5) (2017) 2713–2719.
[41] Q. Yao, et al., MicroRNA-21 promotes cell proliferation and down-regulates the expression of programmed cell death 4 (PDCD4) in HeLa cervical carcinoma cells, Biochem. Biophys. Res. Commun. 388 (3) (2009) 539–542.
[42] B. Lankat-Buttgereit, R. Göke, The tumour suppressor Pdcd4: recent advances in the elucidation of function and regulation, Biol. Cell. 101 (6) (2009) 309–317.
[43] Y. Wang, B. Dai, PTEN genomic deletion defines favorable prognostic biomarkers in localized prostate cancer: a systematic review and meta-analysis, Int. J. Clin. Exp. Med. 8 (4) (2015) 5430–5437.
[44] H.H. Zhang, et al., miR-21 inhibits autophagy and promotes malignant development in the bladder cancer T24 cell line, Int. J. Oncol. 56 (4) (2020) 986–998.
[45] T. Yao, et al., Growth arrest-specific 5 attenuates cisplatin-induced apoptosis in cervical cancer by regulating STAT3 signaling via miR-21, J. Cell. Physiol. 234 (6) (2019) 9605–9615.
[46] Y. Tay, J. Rinn, P.P. Pandolfi, The multilayered complexity of ceRNA crosstalk and competition, Nature 505 (7483) (2014) 344–352.
[47] J. Xu, et al., The role of lncRNA-mediated ceRNA regulatory networks in pancreatic cancer, Cell Death Dis. 8 (1) (2022) 287.
[48] W. Wang, et al., A novel mRNA-miRNA-lncRNA competing endogenous RNA triple sub-network associated with prognosis of pancreatic cancer, Aging (Albany NY) 11 (9) (2019) 2610–2627.
[49] H. Zhang, et al., MiR-7, inhibited indirectly by lincRNA HOTAIR, directly inhibits SETDB1 and reverses the EMT of breast cancer stem cells by downregulating the STAT3 pathway, Stem Cell. 32 (11) (2014) 2858–2868.
[50] X. Zhou, et al., The interaction between MiR-141 and lncRNA-H19 in regulating cell proliferation and migration in gastric cancer, Cell. Physiol. Biochem. 36 (4) (2015) 1440–1452.
[51] T. Li, et al., Amplification of long noncoding RNA ZFAS1 promotes metastasis in hepatocellular carcinoma, Cancer Res. 75 (15) (2015) 3181–3191.
[52] J. Liz, M. Esteller, lncRNAs and microRNAs with a role in cancer development, Biochim. Biophys. Acta 1859 (1) (2016) 169–176.
[53] M. Sebastian-delaCruz, et al., The role of lncRNAs in gene expression regulation through mRNA stabilization, Noncoding RNA 7 (1) (2021).
[54] G. Wang, et al., Long non-coding RNA CASC7 suppresses malignant behaviors of breast cancer by regulating miR-21-5p/FASLG axis, Bioengineered 12 (2) (2021) 11555–11566.
[55] A.R. Rama, et al., Circular sponge against miR-21 enhances the antitumor activity of doxorubicin against breast cancer cells, Int. J. Mol. Sci. 23 (23) (2022).
[56] J. Gao, et al., Long non-coding RNA BRE-AS1 inhibits the proliferation, migration, and invasion of cancer cells in triple-negative breast cancer and predicts patients' survival by downregulating miR-21, BMC Cancer 21 (1) (2021) 745.
[57] C.Y. Kadam, S.A. Abhang, Apoptosis markers in breast cancer therapy, Adv. Clin. Chem. 74 (2016) 143–193.
[58] O. Huang, et al., FASLG T844C polymorphism and susceptibility to breast cancer: a meta-analysis, Tumor Biol. 35 (2014) 1089–1094.
[59] L. Yin, et al., Triple-negative breast cancer molecular subtyping and treatment progress, Breast Cancer Res. 22 (2020) 1–13.
[60] H. Fang, et al., miRNA-21 promotes proliferation and invasion of triple-negative breast cancer cells through targeting PTEN, Am. J. Tourism Res. 9 (3) (2017) 953.
[61] M. Zhang, et al., Long non-coding RNA BRE-AS1 represses non-small cell lung cancer cell growth and survival via up-regulating NR4A3, Arch. Biochem. Biophys. 660 (2018) 53–63.
[62] Z. Chen, M. Zhen, J. Zhou, LncRNA BRE-AS1 interacts with miR-145-5p to regulate cancer cell proliferation and apoptosis in prostate carcinoma and has early diagnostic values, Biosci. Rep. 39 (3) (2019).
[63] M. Zhu, et al., MEG3 overexpression inhibits the tumorigenesis of breast cancer by downregulating miR-21 through the PI3K/Akt pathway, Arch. Biochem. Biophys. 661 (2019) 22–30.
[64] B. Jiang, Aerobic glycolysis and high level of lactate in cancer metabolism and microenvironment, Genes Dis. 4 (1) (2017) 25–27.
[65] Y. Feng, et al., Modulation of CASC2/miR-21/PTEN pathway sensitizes cervical cancer to cisplatin, Arch. Biochem. Biophys. 623–624 (2017) 20–30.
[66] Y. Du, et al., LncRNA MEG3 promotes cisplatin sensitivity of cervical cancer cells by regulating the miR-21/PTEN axis, BMC Cancer 22 (1) (2022) 1145.
[67] J. Zhang, et al., Long noncoding RNA MEG3 is downregulated in cervical cancer and affects cell proliferation and apoptosis by regulating miR-21, Cancer Biol. Ther. 17 (1) (2016) 104–113.
[68] H. Bai, X. Li, S. Wu, Up-regulation of long non-coding RNA LOXL1-AS1 functions as an oncogene in cervical squamous cell carcinoma by sponging miR-21, Arch. Physiol. Biochem. 129 (1) (2023) 143–147.
[69] Y. Wang, et al., MicroRNA-21 and its impact on signaling pathways in cervical cancer, Oncol. Lett. 17 (3) (2019) 3066–3070.
[70] T. Yao, Z. Lin, MiR-21 is involved in cervical squamous cell tumorigenesis and regulates CCL20, Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1822 (2) (2012) 248–260.
[71] E.J. Crosbie, et al., Endometrial cancer, Lancet 399 (10333) (2022) 1412–1428.
[72] V. Makker, et al., Endometrial cancer, Nat. Rev. Dis. Prim. 7 (1) (2021) 88.
[73] B.L. Li, X.P. Wan, The role of lncRNAs in the development of endometrial carcinoma, Oncol. Lett. 16 (3) (2018) 3424–3429.
[74] H. Ding, et al., Prediction of clinical outcome in endometrial carcinoma based on a 3-lncRNA signature, Front. Cell Dev. Biol. 9 (2022) 3963.
[75] A. Bouziyane, et al., Diagnostic value of MicroRNA 21 in endometrial cancer and benign lesions and its differential expression with clinicopathological parameters, MicroRNA 10 (2) (2021) 146–152.
[76] K. Sato, et al., MicroRNA-21 expression in cancer cells is an independent biomarker of progression-free survival of endometrioid endometrial carcinoma, Virchows Arch. 479 (2021) 883–891.
[77] M. Liang, et al., LncRNA RUNX1-IT1 is downregulated in endometrial cancer and binds to miR-21 precursor to suppress its maturation, Cancer Manag. Res. 12 (2020) 13451–13459.
[78] C. Tian, et al., lncRNA NBAT1 inhibits cell metastasis and promotes apoptosis in endometrial cancer by sponging miR-21-5p to regulate PTEN, Comput. Math. Methods Med. 2022 (2022) 9304392.
[79] C.A. Doubeni, A.R. Doubeni, A.E. Myers, Diagnosis and management of ovarian cancer, Am. Fam. Physician 93 (11) (2016) 937–944.
[80] N. Ma, et al., Long non-coding RNA GAS5 inhibits ovarian cancer cell proliferation via the control of microRNA-21 and SPRY2 expression, Exp. Ther. Med. 16 (1) (2018) 73–82.
[81] W. Fang, Y. Xia, LncRNA HLA-F-AS1 attenuates the ovarian cancer development by targeting miR-21-3p/PEG3 axis, Anti Cancer Drugs 33 (7) (2022) 671–681.
[82] J. Xie, et al., LncRNA GAS5 suppresses colorectal cancer progress by target miR-21/LIFR Axis, Evid. Based Complement. Alternat. Med. 2022 (2022) 3298939.
[83] B. Ricciuti, et al., Long noncoding RNAs: new insights into non-small cell lung cancer biology, diagnosis and therapy, Med. Oncol. 33 (2) (2016) 18.
[84] W.-K. So, et al., Loss of Sprouty2 in human high-grade serous ovarian carcinomas promotes EGF-induced E-cadherin down-regulation and cell invasion, FEBS Lett. 589 (3) (2015) 302–309.
[85] S. Masoumi-Moghaddam, et al., S prouty 2 protein, but not S prouty 4, is an independent prognostic biomarker for human epithelial ovarian cancer, Int. J. Cancer 137 (3) (2015) 560–570.
[86] P. Rawla, T. Sunkara, A. Barsouk, Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors, Gastroenterology Review/Przegląd Gastroenterologiczny 14 (2) (2019) 89–103.
[87] A. L Isola, S. Chen, Exosomes: the messengers of health and disease, Curr. Neuropharmacol. 15 (1) (2017) 157–165.
[88] B. Pan, et al., Identification of serum exosomal hsa-circ-0004771 as a novel diagnostic biomarker of colorectal cancer, Front. Genet. 10 (2019) 1096.
[89] A. Shang, et al., Exosomal circPACRGL promotes progression of colorectal cancer via the miR-142-3p/miR-506-3p-TGF-β1 axis, Mol. Cancer 19 (1) (2020) 1–15.
[90] Z. Jiang, et al., Exosomal circEPB41L2 serves as a sponge for miR-21-5p and miR-942-5p to suppress colorectal cancer progression by regulating the PTEN/AKT signalling pathway, Eur. J. Clin. Invest. 51 (9) (2021) e13581.
[91] D. Waniczek, et al., Assessment of PI3K/AKT/PTEN signaling pathway activity in colorectal cancer using quantum dot-conjugated antibodies, Oncol. Lett. 15 (1) (2018) 1236–1240.
[92] X. Li, et al., [Retracted] MicroRNA-760 inhibits cell proliferation and invasion of colorectal cancer by targeting the SP1-mediated PTEN/AKT signalling pathway, Mol. Med. Rep. 26 (2) (2022), 1-1.
[93] G. Li, et al., LINC00312 represses proliferation and metastasis of colorectal cancer cells by regulation of miR-21, J. Cell Mol. Med. 22 (11) (2018) 5565–5572.
[94] H. Huang, et al., lncRNA DGCR5 inhibits the proliferation of colorectal cancer cells by downregulating miR-21, Oncol. Lett. 18 (3) (2019) 3331–3336.
[95] M. Simonian, et al., Evaluation of miR-21 inhibition and its impact on cancer susceptibility candidate 2 long noncoding RNA in colorectal cancer cell line, Adv. Biomed. Res. 7 (2018) 14.
[96] N. Ebrahimi, et al., LncRNA LOC100507144 acts as a novel regulator of CD44/Nanog/Sox2/miR-302/miR-21 axis in colorectal cancer, Biofactors 48 (1) (2022) 164–180.
[97] B. Huang, X. Guo, Y. Li, lncRNA MALAT1 regulates the expression level of miR-21 and interferes with the biological behavior of colon cancer cells, J. BUON 25 (2) (2020) 907–913.
[98] J.H. He, et al., The CircRNA-ACAP2/hsa-miR-21-5p/Tiam1 regulatory feedback circuit affects the proliferation, migration, and invasion of colon cancer SW480 cells, Cell. Physiol. Biochem. 49 (4) (2018) 1539–1550.
[99] J. Huang, et al., Tiam1 is associated with hepatocellular carcinoma metastasis, Int. J. Cancer 132 (1) (2013) 90–100.
[100] A.E. Whiteley, et al., Leukaemia: a model metastatic disease, Nat. Rev. Cancer 21 (7) (2021) 461–475.
[101] Z. Yuan, et al., lncRNA TP73-AS1 regulates miR-21/PTEN Axis to affect cell proliferation in acute myeloid leukemia, Cancer Biother. Radiopharm. 36 (3) (2021) 268–272.
[102] H. Li, et al., LncRNA SCIRT is downregulated in acute myeloid leukemia and sponges miR-21 in cytoplasm to increase chemosensitivity to doxorubicin, Crit. Rev. Eukaryot. Gene Expr. 32 (3) (2022).
[103] P.K. Bhamidipati, et al., Management of imatinib-resistant patients with chronic myeloid leukemia, Therapeutic Adv. Hematol. 4 (2) (2013) 103–117.
[104] X. Zhou, et al., LncRNA MEG3 regulates imatinib resistance in chronic myeloid leukemia via suppressing MicroRNA-21, Biomol. Ther. (Seoul) 25 (5) (2017) 490–496.
[105] F. Siddiqui, Lung Cancer (2022).
[106] S. RM, Non-Coding RNAs in Lung Tumor Initiation and Progression, 2020.
[107] B. He, miRNA-based Biomarkers, Therapies, and Resistance in Cancer, 2020.
[108] W. Zheng, MicroRNA-21: A Promising Biomarker for the Prognosis and Diagnosis of Non-small Cell Lung Cancer, 2018.
[109] C. Pop-Bica, The Clinical Utility of miR-21 and Let-7 in Non-small Cell Lung Cancer (NSCLC). A Systematic Review and Meta-Analysis, 2020.

[110] S. Rai, The Diagnostic Role of microRNA 21 in Patients with Nonsmall Cell Lung Cancer: an Exploratory Study, 2020.
[111] A.R. Rama, Synthetic Circular miR-21 Sponge as Tool for Lung Cancer Treatment, 2022.
[112] K. Ni, miR-21 Promotes Non-small Cell Lung Cancer Cells Growth by Regulating Fatty Acid Metabolism, 2019.
[113] D. Bautista-Sánchez, The Promising Role of miR-21 as a Cancer Biomarker and its Importance in RNA-Based Therapeutics, 2020.
[114] D. Wang, LncRNA SNHG9 Is Downregulated in Non-small Cell Lung Cancer and Suppressed miR-21 through Methylation to Promote Cell Proliferation, 2020.
[115] L. Chen, Long Non-coding RNA GAS5 Increases the Radiosensitivity of A549 Cells through Interaction with the miR-21/PTEN/Akt axis, 2020.
[116] M.-M. Georgescu, PTEN tumor suppressor network in PI3K-Akt pathway control, Genes & cancer 1 (12) (2010) 1170–1177.
[117] K. Okamoto, Different Mechanisms of Cisplatin Resistance Development in Human Lung Cancer Cells, 2020.
[118] L. Cao, GAS5 Knockdown Reduces the Chemo-Sensitivity of Non-small Cell Lung Cancer (NSCLC) Cell to Cisplatin (DDP) through Regulating miR-21/PTEN axis, 2017.
[119] S. Li, MicroRNA-21 Promotes the Proliferation, Migration and Invasion of Non-small Cell Lung Cancer A549 Cells by Regulating Autophagy Activity via AMPK/ULK1 Signaling Pathway, 2018.
[120] J.-g. Zhang, MicroRNA-21 (miR-21) Represses Tumor Suppressor PTEN and Promotes Growth and Invasion in Non-small Cell Lung Cancer (NSCLC), 2010.
[121] L. Li, Long Non-coding RNA CASC2 Enhanced Cisplatin-Induced Viability Inhibition of Non-small Cell Lung Cancer Cells by Regulating the PTEN/PI3K/Akt Pathway through Down-Regulation of miR-18a and miR-21, 2018.
[122] Palmieri, G., *Long Non-Coding RNA CASC2 in Human Cancer* 2017.
[123] S. Ghafouri-Fard, The Role of Long Non-coding RNA CASC2 in the Carcinogenesis Process, 2020.
[124] Z.-H. Wu, LncRNA CASC2 Inhibits Lung Adenocarcinoma Progression through Forming Feedback Loop with miR-21/p53 axis, 2021.
[125] D. Lv, Long Non-coding RNA MEG3 Inhibits Cell Migration and Invasion of Non-small Cell Lung Cancer Cells by Regulating the miR-21-5p/PTEN axis, 2021.
[126] D. Lv, Long Non-coding RNA MEG3 Inhibits Cell Migration and Invasion of Non-small Cell Lung Cancer Cells by Regulating the miR-21-5p/PTEN axis, 2016.
[127] P. Wang, LncRNA MEG3 enhances cisplatin sensitivity, in: Non-Small Cell Lung Cancer by Regulating miR-21-5p/SOX7 axis, 2017.
[128] H. Xia, LncRNA PLAC 2 Downregulated miR-21 in Non-small Cell Lung Cancer and Predicted Survival, 2019.
[129] Y. Zhu, LINC00968 Can Inhibit the Progression of Lung Adenocarcinoma through the miR-21-5p/SMAD7 Signal axis, 2020.
[130] B.B. Ordys, et al., The role of mitochondria in glioma pathophysiology, Mol. Neurobiol. 42 (1) (2010) 64–75.
[131] L.P. Taylor, Diagnosis, treatment, and prognosis of glioma: five new things, Neurology 75 (18 Suppl 1) (2010) S28–S32.
[132] T. Stokland, et al., A multivariate analysis of factors determining tumor progression in childhood low-grade glioma: a population-based cohort study (CCLG CNS9702), Neuro Oncol. 12 (12) (2010) 1257–1268.
[133] S. D, The Role of CASC2 and miR-21 Interplay in Glioma Malignancy and Patient Outcome, 2020.
[134] N. Guan, Long Non-coding RNA NBAT1 Inhibits the Progression of Glioma through the miR-21/SOX7 axis, 2020.
[135] M. H, Potential Therapeutic Effects of Exosomes Packed with a miR-21-Sponge Construct in a Rat Model of Glioblastoma, 2019.
[136] Z. He, LncRNA DGCR5 Plays a Tumor-Suppressive Role in Glioma via the miR-21/Smad7 and miR-23a/PTEN Axes, 2020.
[137] J. Jiang, PWRN1 Suppressed Cancer Cell Proliferation and Migration in Glioblastoma by Inversely Regulating Hsa-miR-21-5p, 2020.
[138] W.-X. Qin, EZH2-mediated H3K27me3 Enrichment on the lncRNA MEG3 Promoter Regulates the Growth and Metastasis of Glioma Cells by Regulating miR-21-3p, 2020.
[139] P. Wang, Long Non-Coding RNA CASC2 Suppresses Malignancy in Human Gliomas by miR-21, 2015.
[140] Z. He, et al., LncRNA DGCR5 plays a tumor-suppressive role in glioma via the miR-21/Smad7 and miR-23a/PTEN axes, Aging (Albany NY) 12 (20) (2020) 20285–20307.
[141] J. Yu, MicroRNA-182 Targets SMAD7 to Potentiate TGFβ-Induced Epithelial-Mesenchymal Transition and Metastasis of Cancer Cells, 2016.
[142] N. Guan, et al., Long non-coding RNA NBAT1 inhibits the progression of glioma through the miR-21/SOX7 axis, Oncol. Lett. 20 (3) (2020) 3024–3034.
[143] Z. Chen, et al., Prader–Willi region non-protein coding RNA 1 suppressed gastric cancer growth as a competing endogenous RNA of miR-425-5p, Clin. Sci. 132 (9) (2018) 1003–1019.
[144] Y.S. Bogliotti, P.J. Ross, Mechanisms of histone H3 lysine 27 trimethylation remodeling during early mammalian development, Epigenetics 7 (9) (2012) 976–981.
[145] P. Das, J.H. Taube, Regulating methylation at H3K27: a trick or treat for cancer cell plasticity, Cancers 12 (10) (2020) 2792.
[146] L. Gan, et al., Epigenetic regulation of cancer progression by EZH2: from biological insights to therapeutic potential, Biomark. Res. 6 (1) (2018) 1–10.
[147] A. Hao, et al., Emerging roles of lncRNAs in the EZH2-regulated oncogenic network, Int. J. Biol. Sci. 17 (13) (2021) 3268.
[148] F. Hanif, et al., Glioblastoma multiforme: a review of its epidemiology and pathogenesis through clinical presentation and treatment, Asian Pac. J. Cancer Prev. APJCP: Asian Pac. J. Cancer Prev. APJCP 18 (1) (2017) 3.
[149] a. C, Oral Cavity and Oropharyngeal Squamous CellCarcinoma, 2015.
[150] T. Flügge, Detection of Oral Squamous Cell Carcinoma in Clinical Photographs Using a Vision Transformer, 2023.
[151] J. Bernier, Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer, 2004.
[152] Y. Tutar, Pseudogenes, Int. J. Genomics (2012) 2012.
[153] X. Hu, L. Yang, Y.-Y. Mo, Role of pseudogenes in tumorigenesis, Cancers 10 (8) (2018) 256.
[154] L. Poliseno, et al., A coding-independent function of gene and pseudogene mRNAs regulates tumour biology, Nature 465 (7301) (2010) 1033–1038.
[155] L. Gao, PTENp1, a Natural Sponge of miR-21, Mediates PTEN Expression to Inhibit the Proliferation of Oral Squamous Cell Carcinoma, 2016.
[156] B. Zeng, LncRNA GAS5 Suppresses Proliferation, Migration, Invasion, and Epithelial-Mesenchymal Transition in Oral Squamous Cell Carcinoma by Regulating the miR-21/PTEN axis, 2019.
[157] L.-L. Zhang, Low Expression of lncRNA MEG3 Promotes the Progression of Oral Squamous Cell Carcinoma by Targeting miR-21, 2018.
[158] D.-C. Lin, Genomic and Epigenomic Aberrations in Esophageal Squamous Cell Carcinoma and Implications for Patients, 2018.
[159] R. L, Cancer Statistics, 2019.
[160] H. Kashima, Cancer-associated Fibroblasts (CAFs) Promote the Lymph Node Metastasis of Esophageal Squamous Cell Carcinoma, 2018.
[161] M. Muto, Early Detection of Superficial Squamous Cell Carcinoma in the Head and Neck Region and Esophagus by Narrow Band Imaging: A Multicenter Randomized Controlled Trial, 2010.
[162] M. Hemmatzadeh, et al., Differential role of microRNAs in the pathogenesis and treatment of Esophageal cancer, Biomed. Pharmacother. 82 (2016) 509–519.
[163] Z. Wang, Synthetic Circular Multi-miR Sponge Simultaneously Inhibits miR-21 and miR-93 in Esophageal Carcinoma, 2019.
[164] B. Wang, *LncRNA-IUR Up-Regulates PTEN by Sponging miR-21 to Regulate Cancer Cell Proliferation and Apoptosis in Esophageal Squamous Cell Carcinoma*, 2020.
[165] F. Bray, Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, 2018.
[166] R.L. Siegel, Cancer Statistics, 2019.
[167] S.-Y. Zhang, Retrospective Analysis of Prognostic Factors in 205 Patients with Laryngeal Squamous Cell Carcinoma Who Underwent Surgical Treatment, 2013.
[168] E.M. Graboyes, Evaluation of Quality Metrics for Surgically Treated Laryngeal Squamous Cell Carcinoma, 2016.
[169] N. Gale, Laryngeal Squamous Intraepithelial Lesions: an Updated Review on Etiology, Classification, Molecular Changes, and Treatment, 2016.
[170] W.X. MD, LncRNA miR143HG Suppresses miR-21 through Methylation to Inhibit Cell Invasion and Migration, 2019.
[171] K. Lyu, Long Noncoding RNA GAS5 Acts as A Tumor Suppressor in Laryngeal Squamous Cell Carcinoma via miR-21, 2019.
[172] Y. S, Histology, Thyroid Gland, 2022.
[173] M.E. Cabanillas, D.G. McFadden, C. Durante, Thyroid cancer, Lancet 388 (10061) (2016) 2783–2795.
[174] F. Limaiem, A. Rehman, T. Mazzoni, Papillary Thyroid Carcinoma, 2019.
[175] Y. Li, Knockdown of circPUM1 Impedes Cell Growth, Metastasis and Glycolysis of Papillary Thyroid Cancer via Enhancing MAPK1 Expression by Serving as the Sponge of miR-21-5p, 2021.
[176] Q.T. Pham, et al., The expression of BTS-2 enhances cell growth and invasiveness in renal cell carcinoma, Anticancer Res. 37 (6) (2017) 2853–2860.
[177] K.H. Fang, et al., Overexpression of BST2 is associated with nodal metastasis and poorer prognosis in oral cavity cancer, Laryngoscope 124 (9) (2014) E354–E360.
[178] H. Zhang, LncRNA BISPR Promotes the Progression of Thyroid Papillary Carcinoma by Regulating miR-21-5p, 2018.
[179] Z. Wang, OTUD6B-AS1 inhibits viability. Migration, and Invasion of Thyroid Carcinoma by Targeting miR-183-5p and miR-21, 2020.
[180] A. Villanueva, et al., Hepatocellular carcinoma: novel molecular approaches for diagnosis, prognosis, and therapy, Annu. Rev. Med. 61 (2010) 317–328.
[181] V.C. Sun, L. Sarna, Symptom management in hepatocellular carcinoma, Clin. J. Oncol. Nurs. 12 (5) (2008) 759–766.
[182] J. Balogh, et al., Hepatocellular carcinoma: a review, J. Hepatocell. Carcinoma 3 (2016) 41–53.
[183] L. Gramantieri, et al., MicroRNA involvement in hepatocellular carcinoma, J. Cell Mol. Med. 12 (6a) (2008) 2189–2204.
[184] J. Sun, et al., Long non-coding RNAs: critical players in hepatocellular carcinoma, Int. J. Mol. Sci. 15 (11) (2014) 20434–20448.
[185] L. Hu, et al., Long noncoding RNA GAS5 suppresses the migration and invasion of hepatocellular carcinoma cells via miR-21, Tumour Biol. 37 (2) (2016) 2691–2702.
[186] J. Ji, et al., The role of long non-coding RNA GAS5 in cancers, Cancer Manag. Res. 11 (2019) 2729–2737.
[187] L.F. Xu, et al., MicroRNA-21 (miR-21) regulates cellular proliferation, invasion, migration, and apoptosis by targeting PTEN, RECK and Bcl-2 in lung squamous carcinoma, Gejiu City, China, PLoS One 9 (8) (2014) e103698.
[188] M. Sun, et al., Decreased expression of long noncoding RNA GAS5 indicates a poor prognosis and promotes cell proliferation in gastric cancer, BMC Cancer 14 (2014) 319.
[189] W.Y. Wang, et al., miR-21 expression predicts prognosis in hepatocellular carcinoma, Clin. Res. Hepatol. Gastroenterol. 38 (6) (2014) 715–719.
[190] Q. Yang, G. Wu, CircRNA-001241 mediates sorafenib resistance of hepatocellular carcinoma cells by sponging miR-21-5p and regulating TIMP3 expression, Gastroenterol. Hepatol. 45 (10) (2022) 742–752.

[191] W. Li, et al., LncRNA SNHG1 contributes to sorafenib resistance by activating the Akt pathway and is positively regulated by miR-21 in hepatocellular carcinoma cells, J. Exp. Clin. Cancer Res. 38 (1) (2019) 183.
[192] A. Ben Mousa, Sorafenib in the treatment of advanced hepatocellular carcinoma, Saudi J. Gastroenterol. 14 (1) (2008) 40–42.
[193] W. Tang, et al., The mechanisms of sorafenib resistance in hepatocellular carcinoma: theoretical basis and therapeutic aspects, Signal Transduct. Targeted Ther. 5 (1) (2020) 87.
[194] B. Zhai, et al., Inhibition of Akt reverses the acquired resistance to sorafenib by switching protective autophagy to autophagic cell death in hepatocellular carcinoma, Mol. Cancer Therapeut. 13 (6) (2014) 1589–1598.
[195] C. He, et al., MiR-21 mediates sorafenib resistance of hepatocellular carcinoma cells by inhibiting autophagy via the PTEN/Akt pathway, Oncotarget 6 (30) (2015) 28867–28881.
[196] Q. Du, J. Chen, SNHG1 promotes proliferation, migration and invasion of bladder cancer cells via the PI3K/AKT signaling pathway, Exp. Ther. Med. 20 (5) (2020) 110.
[197] Y. Sun, et al., The long noncoding RNA SNHG1 promotes tumor growth through regulating transcription of both local and distal genes, Oncogene 36 (49) (2017) 6774–6783.
[198] Q. Lu, et al., Long noncoding RNA SNHG1 promotes non-small cell lung cancer progression by up-regulating MTDH via sponging miR-145-5p, Faseb. J. 32 (7) (2018) 3957–3967.
[199] K. Brew, H. Nagase, The tissue inhibitors of metalloproteinases (TIMPs): an ancient family with structural and functional diversity, Biochim. Biophys. Acta 1803 (1) (2010) 55–71.
[200] E. Morgan, et al., The current and future incidence and mortality of gastric cancer in 185 countries, 2020-40: a population-based modelling study, EClinicalMedicine 47 (2022) 101404.
[201] M. Palrasu, et al., Role of bacterial and viral pathogens in gastric carcinogenesis, Cancers 13 (8) (2021).
[202] R.E. Sexton, et al., Gastric cancer: a comprehensive review of current and future treatment strategies, Cancer Metastasis Rev. 39 (4) (2020) 1179–1203.
[203] R.E. Sexton, et al., Gastric cancer: a comprehensive review of current and future treatment strategies, Cancer Metastasis Rev. 39 (4) (2020) 1179–1203.
[204] R. Sitarz, et al., Gastric cancer: epidemiology, prevention, classification, and treatment, Cancer Manag. Res. 10 (2018) 239–248.
[205] W. Li, et al., The long noncoding RNA, growth arrest-specific 5, suppresses gastric cancer by downregulating miR-21 expression, Pharmacology 105 (7–8) (2020) 434–444.
[206] G. Xu, et al., MEG3/miR-21 axis affects cell mobility by suppressing epithelial-mesenchymal transition in gastric cancer, Oncol. Rep. (2018).
[207] D. Ribatti, R. Tamma, T. Annese, Epithelial-mesenchymal transition in cancer: a historical overview, Translational Oncol. 13 (6) (2020) 100773.
[208] X. Liu, et al., Synthetic circular RNA functions as a miR-21 sponge to suppress gastric carcinoma cell proliferation, Mol. Ther. Nucleic Acids 13 (2018) 312–321.
[209] A.L. Pereira, et al., The biological role of sponge circular RNAs in gastric cancer: main players or coadjuvants? Cancers 12 (7) (2020).
[210] T.B. Hansen, et al., Natural RNA circles function as efficient microRNA sponges, Nature 495 (7441) (2013) 384–388.
[211] J. Han, et al., Circ_0027599 elevates RUNX1 expression via sponging miR-21-5p on gastric cancer progression, Eur. J. Clin. Invest. 51 (11) (2021) e13592.
[212] E. Guan, H. Liu, N. Xu, Lidocaine suppresses gastric cancer development through Circ_ANO5/miR-21-5p/LIFR Axis, Dig. Dis. Sci. 67 (6) (2022) 2244–2256.
[213] F. Zhang, et al., Pan-cancer analysis identifies LIFR as a prognostic and immunological biomarker for uterine corpus endometrial carcinoma, Front. Oncol. 13 (2023) 1118906.
[214] W. Zeng, et al., Lidocaine suppresses the malignant behavior of gastric cancer cells via the c-Met/c-Src pathway, Exp. Ther. Med. 21 (5) (2021) 424.
[215] L. Ye, et al., Anti-tumor effects of lidocaine on human gastric cancer cells in vitro, Bratislava Med. J. 120 (3) (2019) 212–217.
[216] H. Sui, et al., Lidocaine inhibits growth, migration and invasion of gastric carcinoma cells by up-regulation of miR-145, BMC Cancer 19 (1) (2019) 233.
[217] D. Chen, et al., LncRNA growth arrest-specific transcript 5 targets miR-21 gene and regulates bladder cancer cell proliferation and apoptosis through PTEN, Cancer Med. 9 (8) (2020) 2846–2858.
[218] Y. Wang, et al., Downregulated lncRNA GAS5 and upregulated miR-21 lead to epithelial–mesenchymal transition and lung metastasis of osteosarcomas, Front. Cell Dev. Biol. 9 (2021) 707693.
[219] X. Zhao, et al., Osteosarcoma: a review of current and future therapeutic approaches, Biomed. Eng. Online 20 (1) (2021) 24.
[220] A. Jamil, A. Kasi, Lung metastasis, in: *StatPearls*. 2023, StatPearls Publishing Copyright ©, StatPearls Publishing LLC., Treasure Island (FL), 2023.
[221] K. Saha, et al., Osteosarcoma relapse as pleural metastasis, South Asian J. Cancer 2 (2) (2013) 56.
[222] H. Zhang, et al., Long non-coding RNA CASC2 upregulates PTEN to suppress pancreatic carcinoma cell metastasis by downregulating miR-21, Cancer Cell Int. 19 (1) (2019) 18.
[223] T.J. Ettrich, et al., Pancreatic cancer: current multimodality treatment options and the future impact of molecular biological profiling, Visc. Med. 38 (1) (2022) 20–29.
[224] L. Wu, et al., LncRNA MEG3 promotes melanoma growth, metastasis and formation through modulating miR-21/E-cadherin axis, Cancer Cell Int. 20 (1) (2020) 12.
[225] K. Eddy, R. Shah, S. Chen, Decoding melanoma development and progression: identification of therapeutic vulnerabilities, Front. Oncol. 10 (2021) 626129.
[226] L.E. Davis, S.C. Shalin, A.J. Tackett, Current state of melanoma diagnosis and treatment, Cancer Biol. Ther. 20 (11) (2019) 1366–1379.
[227] R. Zhang, T. Xia, Long non-coding RNA XIST regulates PDCD4 expression by interacting with miR-21-5p and inhibits osteosarcoma cell growth and metastasis, Int. J. Oncol. 51 (5) (2017) 1460–1470.
[228] Q. Wang, H.S. Yang, The role of Pdcd4 in tumour suppression and protein translation, Biol. Cell. 110 (8) (2018) 169–177.
[229] D. Wang, et al., circSLC8A1 acts as a tumor suppressor in prostate cancer via sponging miR-21, BioMed Res. Int. 2021 (2021) 1–9.
[230] T. Shi, G. Gao, Y. Cao, Long noncoding RNAs as novel biomarkers have a promising future in cancer diagnostics, Dis. Markers 2016 (2016) 9085195.
[231] A. Bahramy, et al., Prognostic and diagnostic values of non-coding RNAs as biomarkers for breast cancer: an umbrella review and pan-cancer analysis, Front. Mol. Biosci. 10 (2023) 1096524.
[232] H. Zhang, et al., LncRNA BISPR promotes the progression of thyroid papillary carcinoma by regulating miR-21-5p, Int. J. Immunopathol. Pharmacol. 32 (2018) 2058738418772652.
[233] L. Li, et al., Long non-coding RNA CASC2 enhanced cisplatin-induced viability inhibition of non-small cell lung cancer cells by regulating the PTEN/PI3K/Akt pathway through down-regulation of miR-18a and miR-21, RSC Adv. 8 (29) (2018) 15923–15932.
[234] Z.H. Wu, et al., LncRNA CASC2 inhibits lung adenocarcinoma progression through forming feedback loop with miR-21/p53 axis, Kaohsiung J. Med. Sci. 37 (8) (2021) 675–685.
[235] D. Skiriute, The Role of CASC2 and miR-21 Interplay in Glioma Malignancy and Patient Outcome, 2020.
[236] E. Guan, H. Liu, N. Xu, Lidocaine suppresses gastric cancer development through Circ_ANO5/miR-21-5p/LIFR Axis, Dig. Dis. Sci. 67 (6) (2022) 2244–2256.
[237] Y. Li, et al., Knockdown of circPUM1 impedes cell growth, metastasis and glycolysis of papillary thyroid cancer via enhancing MAPK1 expression by serving as the sponge of miR-21-5p, Genes Genomics 43 (2) (2021) 141–150.
[238] J. Han, et al., Circ_0027599 elevates RUNX1 expression via sponging miR-21-5p on gastric cancer progression, Eur. J. Clin. Invest. 51 (11) (2021).
[239] Q. Yang, G. Wu, CircRNA-001241 mediates sorafenib resistance of hepatocellular carcinoma cells by sponging miR-21-5p and regulating TIMP3 expression, Gastroenterol. Hepatol. 45 (10) (2022) 742–752.
[240] L. Chen, et al., Long non-coding RNA GAS5 increases the radiosensitivity of A549 cells through interaction with the miR-21/PTEN/Akt axis, Oncol. Rep. 43 (3) (2020) 897–907.
[241] L. Cao, et al., GAS5 knockdown reduces the chemo-sensitivity of non-small cell lung cancer (NSCLC) cell to cisplatin (DDP) through regulating miR-21/PTEN axis, Biomed. Pharmacother. 93 (2017) 570–579.
[242] B. Wang, LncRNA-IUR Up-Regulates PTEN by Sponging miR-21 to Regulate Cancer Cell Proliferation and Apoptosis in Esophageal Squamous Cell Carcinoma, 2020.
[243] Y. Zhu, et al., LINC00968 can inhibit the progression of lung adenocarcinoma through the miR-21-5p/SMAD7 signal axis, Aging (Albany NY) 12 (21) (2020) 21904–21922.
[244] D. Lv, et al., Long non-coding RNA MEG3 inhibits cell migration and invasion of non-small cell lung cancer cells by regulating the miR-21-5p/PTEN axis, Mol. Med. Rep. 23 (3) (2021).
[245] P. Wang, et al., LncRNA MEG3 enhances cisplatin sensitivity in non-small cell lung cancer by regulating miR-21-5p/SOX7 axis, OncoTargets Ther. 10 (2017) 5137–5149.
[246] W.-X. Qin, EZH2-mediated H3K27me3 Enrichment on the lncRNA MEG3 Promoter Regulates the Growth and Metastasis of Glioma Cells by Regulating miR-21-3p, 2020.
[247] W. Xun, LncRNA miR143HG Suppresses miR-21 through Methylation to Inhibit Cell Invasion and Migration, 2020.
[248] Z. Wang, et al., OTUD6B-AS1 inhibits viability, migration, and invasion of thyroid carcinoma by targeting miR-183-5p and miR-21, Front. Endocrinol. 11 (2020) 136.
[249] Y. Cai, et al., LncRNA OTUD6B-AS1 inhibits many cellular processes in colorectal cancer by sponging miR-21-5p and regulating PNRC2, Hum. Exp. Toxicol. 40 (9) (2021) 1463–1473.
[250] H. Xia, et al., LncRNA PLAC 2 downregulated miR-21 in non-small cell lung cancer and predicted survival, BMC Pulm. Med. 19 (1) (2019) 172.
[251] D. Wang, et al., LncRNA SNHG9 is downregulated in non-small cell lung cancer and suppressed miR-21 through methylation to promote cell proliferation, Cancer Manag. Res. 12 (2020) 7941–7948.
[252] S. Tao, et al., Long non-coding RNA T-cell leukemia/lymphoma 6 serves as a sponge for miR-21 modulating the cell proliferation of retinoblastoma through PTEN, KOREAN J. PHYSIOL. PHARMACOL. 23 (6) (2019) 449–458.
[253] X. Zhou, et al., Comprehensive analysis of PTEN-related ceRNA network revealing the key pathways WDFY3-AS2 - miR-21-5p/miR-221-3p/miR-222-3p - TIMP3 as potential biomarker in tumorigenesis and prognosis of kidney renal clear cell carcinoma, Mol. Carcinog. 61 (5) (2022) 508–523.