Function of microRNA-124 in the pathogenesis of cancer (Review)

YUCHEN LIU[1*], YIPIN YANG[2*], XINYI WANG[3*], SIYUE YIN[4], BINGYU LIANG[2], YUCHEN ZHANG[1,2], MIN FAN[1], ZIYUE FU[5], CHUANLU SHEN[2], YANXUN HAN[1], BANGJIE CHEN[4] and QIAN ZHANG[6]

[1]Department of Otolaryngology, Head and Neck Surgery, The First Affiliated Hospital of Anhui Medical University; [2]First Clinical Medical College, Anhui Medical University; Departments of [3]Radiation Oncology, and [4]Oncology, The First Affiliated Hospital of Anhui Medical University; [5]Second Clinical Medical College, Anhui Medical University, Hefei, Anhui 230000; [6]Department of Pharmacy, The Affiliated Bozhou Hospital of Anhui Medical University, Bozhou, Anhui 236000, P.R. China

Received May 9, 2023; Accepted September 12, 2023

DOI: 10.3892/ijo.2023.5594

Abstract. Non-coding RNAs with a length of 22-24 nt are known as microRNAs (miRNAs or miRs), which are critical regulators of protein translation. Over the past 10 years, the roles of miRNAs have been extensively investigated in several human cancer types. There is evidence to indicate that miRNAs regulate gene expression by concentrating on a number of substances that have an impact on the physiology and development of cancer cells. Thus, miRNAs as regarded as effective targets for further studies on the design of novel therapeutic strategies. Hepatocellular carcinoma, breast, prostate, and ovarian cancer are only a few of the cancers that miR-124 suppresses. Furthermore, it has been shown that miR-124 is linked to the development and aggressive spread of malignancies. The aim of the present review was to clarify and highlight the role of miR-124 in the development and progression of cancer, emphasizing recent research illustrating how miR-124 has been used as a therapeutic agent against cancer, as well as the diagnostic potential, regulatory mechanisms and clinical application of miR-124.

Correspondence to: Dr Qian Zhang, Department of Pharmacy, The Affiliated Bozhou Hospital of Anhui Medical University, 3 Xuejia Lane, Qiaocheng, Bozhou, Anhui 236000, P.R. China
E-mail: zhangqian9428@163.com

*Contributed equally

Abbreviations: microRNAs/miRs, microRNAs; BC, breast cancer; HCC, hepatocellular cancer; mRNA, messenger RNA; NEAT1, nuclear enriched abundant transcript 1; UHRF1, ubiquitin-like with PHD and RING finger domain 1; lncRNA XIST, long non-coding RNA X-inactive specific transcript; OS, overall survival; DFS, disease-free survival; EMT, epithelial-mesenchymal transition

Key words: microRNAs, microRNA-124, tumors, biomarker, clinical application

Contents

1. Introduction

According to Torre *et al* (1), cancer can be characterized as a pathological condition in which cellular alterations result in uncontrolled, aberrant cell proliferation, culminating in the formation of tumors. The occurrence of tumors is particularly prevalent in less economically developed countries, which account for ~82% of the global population (1). Globally, an estimated 18.1 million new cancer cases and 9.6 million cancer-related deaths occurred annually over the past years (2-4). Of note, Basuroy *et al* (5) found that humans are susceptible to a variety of types of cancer, many of which initially manifest no symptoms or warning indications. The causes of the formation of benign tumors are not yet clear (5-7). In addition, some clinical studies have indicated that abnormal cell polarity and adhesion play a crucial role in tumor progression and metastasis, since they lead to mobility and invasiveness (8), implying that the increased mobility of cancer cells contributes to the high mortality rates among cancer patients. Surgery, chemotherapy, radiation, immunotherapy, monoclonal antibodies, magnetic nanoparticles, personalized medicine and the inhibition of several proteins and transcription factors are currently used as therapeutic methods to treat cancer (9,10). The survival rates of patients with stage III-IV cancer are low, while the survival rates of patients with the majority of early-stage cancers are generally favorable (11,12). As a result, cancer continues to be one of the most disabling diseases in the world; thus, further advancements in the management and treatment of cancer are urgently required.

Short, single-stranded RNAs known as microRNAs (miRNAs/miRs) are found in nature. They interact with their target messenger RNA (mRNAs) to control gene expression at the post-transcriptional level (13), and were first described in *C. elegans* by Lee *et al* (14) in 1993. It has been demonstrated that miRNAs are essential for a number of crucial biological functions, such as cell proliferation, differentiation, apoptosis, metabolism and immunological responses (15-19). Depending on their functions in various types of tumors, miRNAs are categorized as either oncogenes or tumor suppressor genes (20-22). miR-124 may function as a tumor suppressor in a range of cancer types, according to mounting evidence (23). In addition, miR-124 has been linked to a number of crucial cancer-related processes, such as proliferation, tumor spread, epithelial-mesenchymal transition (EMT), metastasis and the resistance of cells (24,25). For instance, breast cancer (BC) tissues have been shown to exhibit a reduced expression of miR-124 compared with normal tissues. The proliferation and migration of cells may be inhibited by miR-124 overexpression in MDA-MB-231 and MCF-7 cells, and the upregulation miR-124 has been shown to be associated with an increased overall survival (OS) of patients with BC (26).

The present review focused on previous findings associated with the expression patterns of miR-124 in various cancer types, and aimed to discuss the major molecular mechanism and potential clinical application involved in the upregulation or downregulation of miR-124 expression, in an effort to clarify which factors are essential to the etiology of this type of cancer. A flowchart of the literature screening, categorization and summarization of the literature is presented in Fig. S1.

2. miR-124 and its abundant biological functions

miR-124 was originally identified in mice in 2002 (27). Subsequent investigations revealed that miR124 was highly conserved, and was expressed in both complex and simple organisms, such as humans and worms, respectively (28). The three miR-124 genes, miR-124-1 (8p23.1), miR-124-2 (8q12.3) and miR-124-3 (20q13.33), were discovered and localized in a previous study (29). The three different miR-124 family members are produced by methylation modification and are associated with cancer, such as BC (30) and gastric cancer (GC) (31). In recent years, miR-124 has been shown to be involved in inflammatory reactions, differentiation, autophagy and cell proliferations (30,32,33). For instance, Wang *et al* (34) reported that fibroblasts derived from calves and patients with severe pulmonary hypertension had lower levels of miR-124 expression. Hypertensive fibroblast proliferation, and the migration and expression of monocyte chemotactic protein-1 (MCP-1) were all markedly reduced following the overexpression of miR-124, in contrast to the enhanced proliferation, migration and MCP-1 expression of the control fibroblast treated with an anti-miR-124 molecule (34). Of note, miR-124, which is associated with EMT, cell cycle arrest, tumor spread and chemoresistance, is often expressed in low levels in various types of malignant tumors (35-41). Shi *et al* (42) reported that prostate cancer cells have considerably lower levels of miR-124 expression (42). Further research revealed that miR-124 overexpression can suppress tumor development and proliferation by upregulating TP53 and downregulating androgen receptor (AR) expression. Another name for baculoviral IAP repeat containing 3 (BIRC3) is IAP2, a protein that belongs to the IAP family of apoptosis-inhibiting proteins. Gan *et al* (43) concluded that IAP suppressed apoptosis by directly repressing the caspase cascade. Previous research has revealed a high association between BIRC3 and a variety of biological processes in cancer cells (44). A previous study demonstrated that all types of human malignant tumors expressed higher levels of BIRC3 than normal tissues (45). Notably, another study revealed that miR-124 regulated BIRC3 expression in hepatocellular carcinoma (HCC) cells by interacting with the 3'-untranslated region (UTR) of BIRC3 (36). Consequently, miR-124 may function as a tumor suppressor, limiting the development of tumors, and may function as a potential biomarker for cancer patients with a poor prognosis. To fully comprehend the potential therapeutic uses of miR-124, further research is required.

3. Regulatory roles of miR-124 in multiple cancer types

Malignant tumors are caused by aberrant cell growth and proliferation. Tumors are recognized by contemporary medicine as a sort of genetic mutation (46). miRNAs have a significant influence on the onset and progression of cancer, according to mounting data (47). Zhang *et al* (48) revealed miR-124 expression was noticeably downregulated in primary BC tissues, and by specifically targeting the programmed cell death protein 6 (PDCD6), it prevented EMT and the motility of BC cells. Simultaneously, miRNA-124 can also target EPH receptor A2 (EphA2) to inhibit cell motility and proliferation in glioma (49). Notably, it has been found that miR-124 is a highly conserved miRNA involved in a number of biological tumor processes, including cellular differentiation, invasion, apoptosis, metastasis and proliferation (50-52). The aim of the present review was to provide a summary of the research findings on miR-124 in various human malignancies, and to discuss its mechanisms of action and clinical importance in the emergence and growth of tumors. The regulatory mechanisms, expression patterns and functional roles of miR-124 in cancer are illustrated in Fig. 1, while Fig. 2 summarizes regulatory networks of miR-124 repeatedly observed in various tumors. In addition, the regulatory mechanisms and targets of miR-124 in various malignancies are presented in Table I.

BC. Worldwide, BC is the most prevalent malignant illness and the main cause of cancer-related mortality among women. It affects ~12% of women worldwide, including 25% (1.7 million) of patients newly diagnosed with cancer and is responsible for 15% (>0.5 million) of all cancer-related deaths (53,54). Accumulating evidence has suggested that the etiology of BC is predominantly hormonal, with an increased lifetime exposure to endogenous and exogenous hormones related to the development of the disease (55,56). The most severe form of BC occurs when the tumor spreads from the breast tissue to other parts of the body (metastasis), which markedly increases the tumor burden and often leads to a terminal diagnosis (57,58). Recently, early diagnosis and novel treatments for BC have achieved notable advancements, and the OS of patients has also improved. However, tumor recurrence and metastasis remain the main cause of mortality for

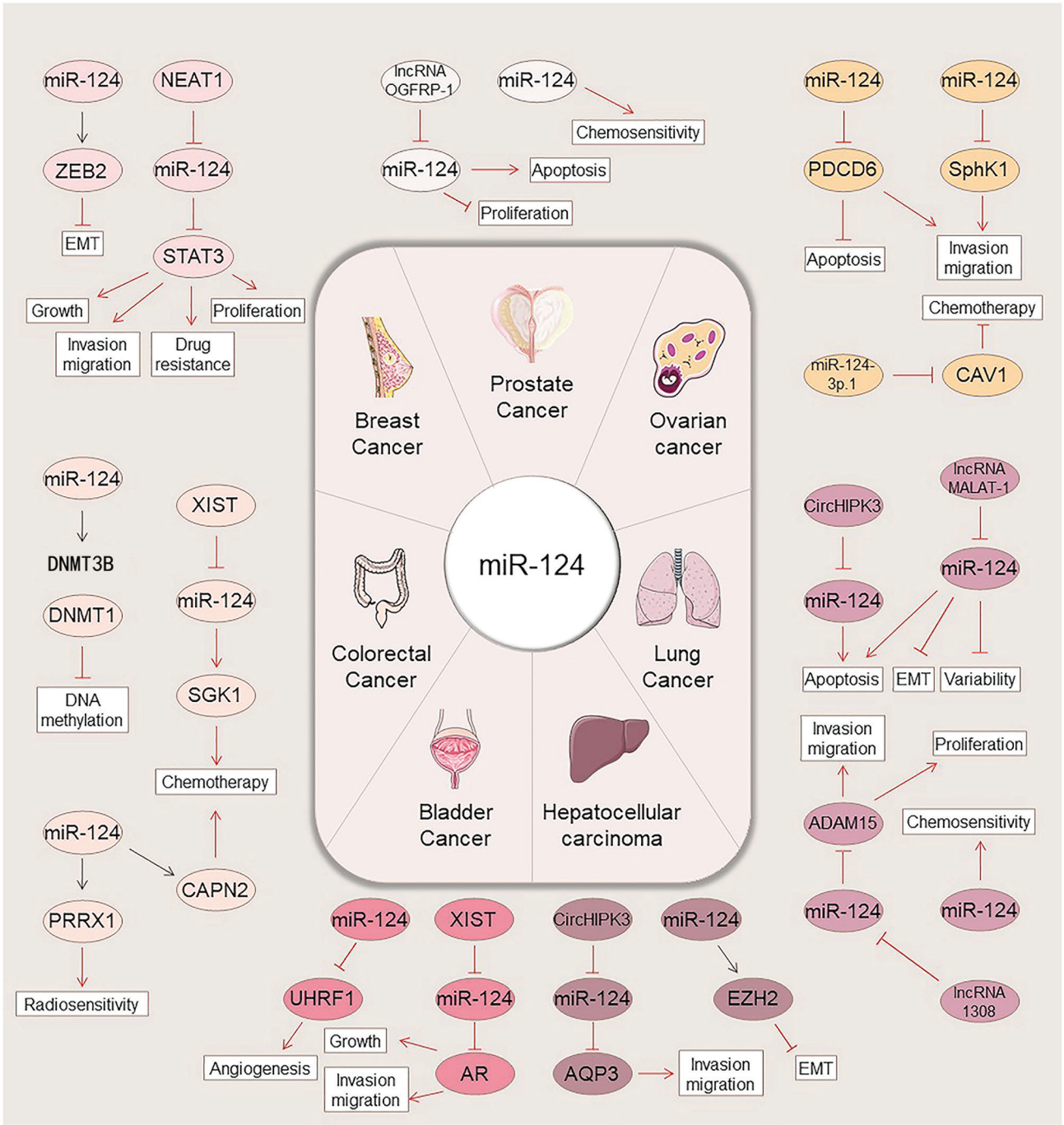

Figure 1. The expression pattern, regulatory mechanism and functional role of microRNA-124 in breast cancer, prostate cancer, ovarian cancer, lung cancer, hepatocellular carcinoma, bladder cancer and colorectal cancer (63,70,85,97,98,109,131,132,143,242-245). NEAT1, nuclear enriched abundant transcript 1; ZEB2, zinc finger E-box binding homeobox 2; EMT, epithelial-mesenchymal transition; DNMT3B, DNA-methyltransferase3B; PRRX1, paired related homeobox 1; XIST, X-inactive specific transcript; SGK1, serum/glucocorticoid regulated kinase 1; CAPN2, calpain 2; UHRF1, ubiquitin-like with PHD and RING finger domain 1; AR, androgen receptor; ADAM15, a disintegrin and metalloproteinase 15; CAV1, caveolin-1. Some of the elements in the figure were derived from *Servier Medical Art* (Web site: *https://smart.servier.com/*) and publication permission was obtained.

a large number of patients with BC, and represent the main obstacles for the reduction of the mortality rates of patients with terminal BC (59,60). In order to increase the OS and disease-free survival (DFS) rates of patients with BC, it may be useful to investigate the biomarkers of BC cell metastasis.

Feng *et al* (61) and Yang *et al* (62) explored the expression of miR-124 in 40 pairs of BC and neighboring non-tumor tissues using reverse transcription-quantitative PCR (RT-qPCR). Compared to the neighboring normal tissues, miR-124 expression in BC tissues was markedly reduced. Furthermore, the expression of miR-124 in the BC cell lines, MCF-7 and MDA-MB-231, was likewise markedly reduced. In addition to resulting in mortality, miR-124 suppression notably decreased BC cell proliferation, migration and invasion *in vivo* and *in vitro* (26). Moreover, miR-124 overexpression has been shown to contribute to an increase in the number of cells present in G_0/G_1 phase from 34.8 to 41.2% (26,62). Of note, Ji *et al* (63) revealed that transfection with miR-124 mimics

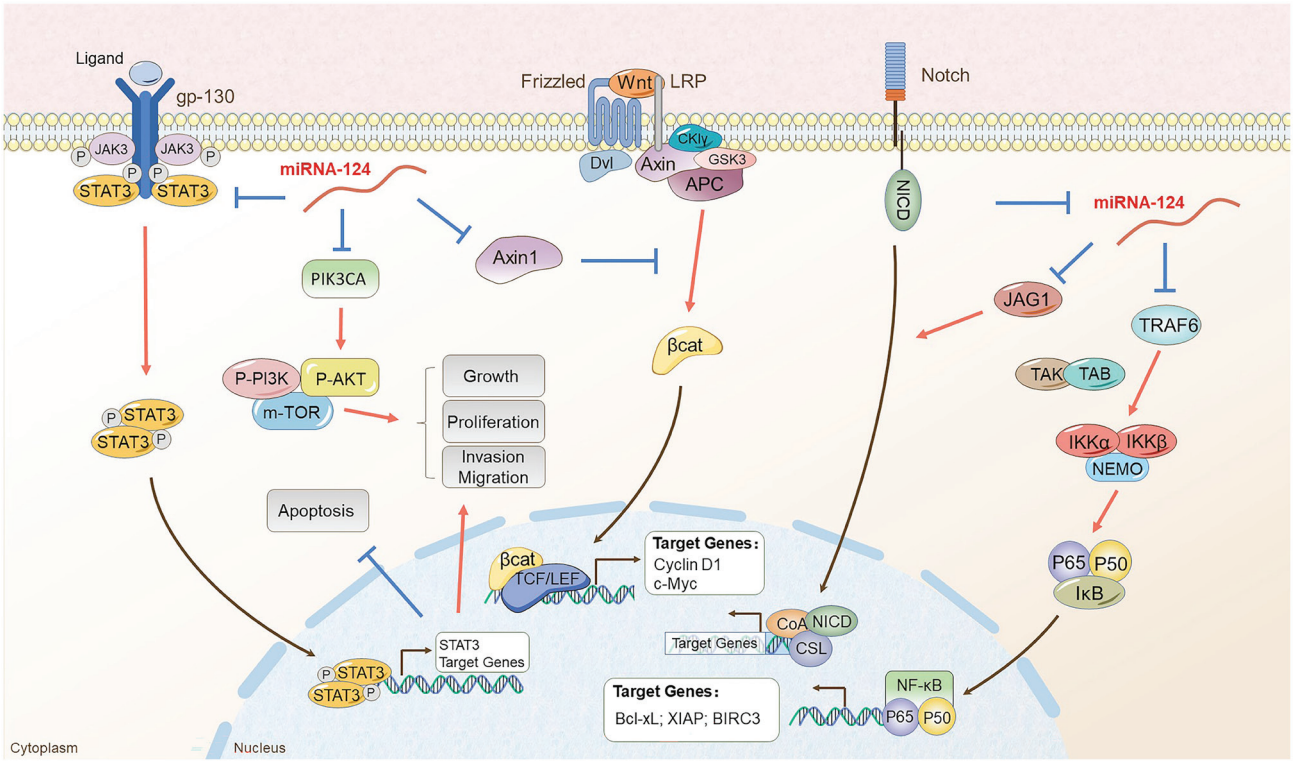

Figure 2. The repeatedly observed regulatory networks of miR-124 detected in different tumor subtypes (62,80,188,246-248). NICD, Notch intracellular domain; Dvl, Dishevelled; JAG1, jagged canonical Notch ligand 1; TRAF6, TNF receptor associated factor 6; BIRC3, baculoviral IAP repeat containing 3. Some of the elements in the figure were derived from *Servier Medical Art* (Web site: *https://smart.servier.com/*) and publication permission was obtained.

significantly increased the expression of the epithelial marker, E-cadherin, in MDA-MB-231 and BT549 cells. However, the expression of the mesenchymal markers, N-cadherin and vimentin, was reduced as a consequence of miR-124 overexpression in MDA-MB-231 and BT549 cells as compared to the control group (63). Simultaneously, the cell shape changed from a fusiform mesenchymal to a polygonal epithelial one when miR-124 was overexpressed in MDA-MB-231 and BT549 cells, demonstrating that the epithelial cell polarity of MDA-MB-231 and BT549 cells was partly regained following transfection with miR-124 mimics (63). It was hypothesized that the anti-metastatic effect of miR-124 was associated with the control of EMT. TargetScan analysis and dual-luciferase reporter assays revealed that a miR-124 binding site was present in the zinc finger E-box binding homeobox 2 (ZEB2) 3'-UTR region, which was later verified to be significantly elevated in BC tissues. Additionally, it was shown that ZEB2 expression in BC tissues was adversely linked with miR-124 expression. miR-124 could suppress EMT via ZEB2, thus further suppressing the metastasis and invasion of BC cells (63). According to the study by Shi *et al* (64), miR-124 may inhibit STAT3 production by interacting with the protein's 3'UTR and controlling the malignant behavior of BC cells. miR-124 is a key modulator of cholinergic anti-inflammatory effects, and it can inhibit the expression of STAT3 and TNF-α converting enzyme (65). Therefore, miR-124 can achieve its antitumor effect by inhibiting these two inflammatory factors. STAT3 is a gene that has been extensively studied in a variety of cancer types. The close interaction between miR-124 and SATA3 makes miR-124 position in anticancer treatment even more critical. STAT3 is closely associated with the proliferation, invasion and natural killer cell tolerance of tumor cells. By suppressing the expression of miR-124, Zhang *et al* (66) reported that LINC00240 caused a number of tumor-promoting behaviors by overexpressing STAT3. Additionally, in another study, rescue experiments revealed that the overexpression of miR-124 had negative effects on cell survival and invasion; however, these effects were substantially reversed by the high expression of STAT3 (64). It has also been found that miR-124 inhibited STAT3 to render BC stem cells less resistant to the therapeutic agent, doxorubicin (DOX), indicating that miR-124 restoration and STAT3 suppression may be an effective combination for combating drug resistance (67). The formation of numerous cancer types has been connected to the nuclear enriched abundant transcript 1 (NEAT1), a new long non-coding RNA (lncRNA) found in nuclear paraspeckles that is essential for sustaining paraspeckles (68). According to the study by Jiang *et al* (69), NEAT1 may target the miR-448/ZEB1 axis to promote the progression of BC. Of note, Pang *et al* (70) demonstrated that NEAT1 functioned as a competitive endogenous RNA (ceRNA) that increased STAT3 expression by sponging miR-124 in BC, and the overexpression of miR-124 attenuated the effects of NEAT1 on the growth of BC cells. Furthermore, the high expression of miR-124 reduced BC cell growth by concentrating on STAT3. In BC tissues, miR-124 levels were inversely linked with NEAT1 and STAT3 expression levels (70). In summary, the aforementioned studies indicate that NEAT1 and STAT3 are connected by a positive feedback loop, which contributes to the proliferation of BC cells. miR-124 is considered to be a key target in the treatment

Table I. Role of miR-124 in various types of cancer.

Cancer type	Change in expression	Cancer cell lines	Function role of miR-124	Relevant upstream therapeutic targets	Relevant downstream therapeutic targets	(Refs.)
Breast cancer	-	MCF-7, MDAMB-435S, BCAP-37, BT549	-	circHIPK3, NEAT1, p62	ZEB2, STAT3, MTDH, EZH2	(26,61-64, 67-73)
Bladder cancer	-	HT-1376, T24, 5637	-	XIST	UHRF1, AR	(37,38,81-83)
Colorectal cancer	-	SW620	-	XIST, YAP1	SGK1, DNMT3B, DNMT1, PRRX1,CAPN2	(39,40,96, 98-100)
Hepatocellular carcinoma	-	Hca-F, HepG2	-	circHIPK3, lncRNA DSCAM-AS1	EZH2, AQP3, PDK2	(103-105,109, 115,117)
Non-small cell lung cancer	-	LTEP-a-2, H226, A549, H460, 95C, 95D, H1299	-	circHIPK3, lncRNA MALAT-1, lncRNA 1308, circPVT1	ADAM15	(124,126, 129-133)
Endometrial cancer	N/A	KYSE-150, KYSE-410	-	lncRNA, NEAT1, STAT3	N/A	(193,194)
Ovarian cancer	-	SKOV3, OCVAR3, HO8910pm	-	LINC00173	PDCD6, SphK1, CAV1, JAG1	(41,142-144)
Prostate cancer	-	PC3, Du145, 22Rv-1, LNCaP, C4-2B, 22Rv1, VCaP	-	N/A	lncRNA QGFRP-1	(150-152)
Gastric cancer	N/A	AGS, HGC-27, NCI-N87, MKN74, GES1	-	lncRNA SND1-IT1	N/A	(195)
Esophageal cancer	N/A	KYSE-150, Eca-109, TE-10, TE-11	-	circVIM	N/A	(214)
Tongue squamous cell carcinoma	N/A	CC25, UM1	-	lncRNA XIST	N/A	(250)
Retinoblastoma	N/A	RCL Y79	-	lncRNA UCA1	N/A	(218)
Melanoma	N/A	SK-MEL-3, A375	-	LNCOC1	N/A	(238)
Osteosarcoma	N/A	Saos-2, U2OS, MG-63, HOS	-	lncRNA FGD5-AS1	G3BP2	(224)
Glioma	N/A	U87MG, U251MG	-	OSMR-AS1	FLOT2	(218)
Cutaneous T-cell lymphoma	N/A	CRL-210, HTB-176	-	lncRNA MALAT1	N/A	(251)
Head and neck squamous cell carcinoma	-	SCC-9, SCC4, CAL27, JHU-13, JHU-22, JHU-29	-	N/A	SphK1, lncRNA PVT1, DNMT1	(160,161)

The '-' symbol indicates reduced expression levels or fuction as a tumor suppressor; N/A, not indicated. CircHIPK3, circRNA homeodomain-interacting protein kinase 3; NEAT1, nuclear enriched abundant transcript 1; p62: Sequestosome 1; XIST, X inactive specific transcript; YAP1, Yes-associated protein 1; lncRNA, long non-coding RNA; DSCAM-AS1, DSCAM antisense RNA1; MALAT-1, metastasis associated lung adenocarcinoma transcript 1; CircPVT, circRNA plasmocytoma variant translocation; LINC00173, long intergenic non-protein coding RNA 173; SND1-IT1, staphylococcal nuclease and tudor domain containing 1-Intronic Transcript 1; CircVIM, circRNA vimentin; UCA1, urothelial cancer associated 1; LNCOC1, lncRNA associated with ovarian cancer 1; FGD5-AS1, FYVE, RhoGEF and PH domain containing 5-antisense RNA 1; OSMR-AS1, oncostatin M receptor-antisense RNA 1; ZEB2, zinc finger E-box binding homeobox 2; STAT3, signal transducer and activator of transcription 3; MTDH, metadherin; EZH2, enhancer of zeste homolog 2; UHRF1, ubiquitin-like with PHD and ring finger domains 1; AR, androgen receptor; SGK1, serum/glucocorticoid regulated kinase 1; DNMT3B, DNA (cytosine-5-)-methyltransferase 3 beta; DNMT1, DNA (cytosine-5-)-methyltransferase 1; PRRX1, paired related homeobox 1; CAPN2, calpain 2; AQP3, aquaporin 3; PDK2, pyruvate dehydrogenase kinase, isozyme 2; ADAM15, ADAM metallopeptidase domain 15; PDCD6, programmed cell death 6; SphK1, sphingosine kinase 1; CAV1, caveolin 1; JAG1, jagged 1; GFRP-1, glass fiber-reinforced polymer-1; G3BP2, GTPase activating protein (SH3 domain) binding protein 2; FLOT2, flotillin 2; PVT1, plasmacytoma variant translocation 1.

of BC. Shi *et al* (71) indicated that circular RNA HIPK3 (circHIPK3) contained in BC cell-derived exosomes increased metadherin expression in endothelial cells by sponging miR-124-3p, thus promoting tube formation in human endothelial cells and potentially serving as a therapeutic target for anti-angiogenesis treatment in BC. The effects of anticancer medications on tumor-associated macrophages (TAMs) may affect their therapeutic efficacy, and the combined use of anticancer drugs with TAM modifiers may be necessary to achieve significant clinical success, according to Wang *et al* (72), who hypothesized that miR-124 could downregulate enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) and thereby promote chemokine ligand 2 expression, thus affecting TAM polarization and infiltration. Guo *et al* (73) identified that an alternatively spliced p62 isoform provided resistance to treatment in BC. These findings increase the current understanding of the molecular processes underlying BC development, and raise the possibility of using miR-124 as a therapeutic target for BC.

Bladder cancer. Bladder cancer is considered one of the most common malignant urinary system cancer types. Bladder cancer is listed as the second highest cause of cancer-related mortality among all genitourinary tumors (74). It is estimated that there are currently 765,950 patients in the USA with bladder cancer (75). Urothelial carcinomas comprise ≤90% of all bladder cancer cases, including invasive and non-invasive bladder cancer. Approximately 15% of urothelial bladder cancer cases may worsen to muscle-invasive cancer (76). Surgery, often an en bloc resection, followed by adjuvant intravenous chemotherapy is the conventional course of treatment for non-muscle invasive bladder cancer (77). The 5-year survival rate for individuals with muscle-invasive cancer is 70%, and the 10-year survival rate is significantly lower (78,79). The highly metastatic nature of bladder cancer is the main reason for its high recurrence and mortality rates. In order to improve the clinical treatment efficiency and patient survival, it is essential to identify effective therapeutic targets and to develop efficient treatment techniques.

miR-124 has been shown to be a crucial regulator of bladder cancer. Previous studies by Zhou *et al* (37) and Zo and Long (38) on miR-124 expression in bladder cancer tissues found that its expression was significantly lower than that in adjacent noncancerous tissues. HT-1376, T24 and 5637 bladder cancer cell lines had considerably lower levels of miR-124 than did SV-HUC-1 normal human bladder epithelial cells. Furthermore, miR-124 overexpression could effectively suppress bladder cancer cell proliferation, while miR-124 downregulation markedly improved the proliferative ability of bladder cancer cells. Compared with the control cells, silencing of miR-124 promoted the invasive and migratory abilities of bladder cancer cells, while these migratory and invasive capacities were impeded by the high expression of miR-124, suggesting that bladder cancer growth and invasion may be inhibited by miR-124. In addition, miR-124 was confirmed to be associated with angiogenesis (80). Vasculogenic mimicry (VM), MMP-2, VEGF and MMP-9 are valid indications of angiogenesis that have been described in previous research (81,82). Wang *et al* (83) observed that miR-124 overexpression notably inhibited the tubular channels formed, and considerably decreased VEGF, MMP-9 and MMP-2 expression levels, thus highlighting the suppressive effects of miR-124 overexpression on bladder cancer angiogenesis. Moreover, the knockdown of miR-124 exerted opposite effects on VM, as well as on the protein level of VEGF, MMP-2 and MMP-9, thus indicating that the ectopic expression if miR-124 can inhibit the angiogenesis of bladder cancer cells (83). Mechanistic analyses demonstrated that miR-124 could interact with ubiquitin-like with PHD and RING finger domain 1 (UHRF1), acting as an important modulator of epigenetic modifications, and significantly decreasing UHRF1 expression in bladder cancer cells. In contrast to UHRF1 overexpression, the aforementioned results demonstrated that miR-124 reduces bladder cancer development, migration, invasion and angiogenesis (83). In several cancer types, lncRNA X-inactive specific transcript (XIST) is associated with cancer progression (84). By controlling the expression of AR, Xiong *et al* (85) demonstrated that the bladder cancer cell proliferation and migration may be affected by XIST; AR is a ligand-dependent transcription factor that regulates biological functions (86). To inhibit the formation of miR-124, XIST can function as a ceRNA. miR-124 may also bind to the protein's 3'-UTR in order to regulate the production of AR (85). miR-124 suppression cab partially override the impact of XIST downregulation on the expression level of AR, c-Myc, p27, MMP-13 and MMP-9 (85), indicating that the newly identified XIST/miR-124/AR axis may regulate bladder cancer cell proliferation, invasion, and migration and may act as a marker and target for bladder cancer patients. The pattern of miR-124 expression in bladder cancer remains unclear, and further studies are required to determine the predictive value of miR-124 and the association between its expression and clinical indicators.

Colorectal cancer (CRC). CRC, which affects >1.2 million individuals per year and is the third highest cause of cancer-related mortality globally, has a 5-year survival rate of 63.5% (87). In 2020, the number of confirmed cases of CRC reached 147,950, and there were 53,200 related deaths. Among patients <50 years of age, 17,930 patients were diagnosed with CRC, and 3,640 patients succumbed to the disease (88). Despite the existence of screening and prevention strategies, due to the frequent occurrence of CRC, it has long been a severe global wellness issue. Despite recent advancements in surgical techniques and comprehensive therapy, CRC is still associated with a poor prognosis, particularly the low long-term survival rate of patients with advanced-stage CRC (89,90). Thus, precise prognosis estimation is essential for physicians, in order to improve and individualize therapeutic strategies. Any novel prognostic signal needs to be verified due to the poor prognosis of patients with CRC.

Zhou *et al* (39) and Taniguchi *et al* (40) investigated the expression profile of miR-124 in CRC tissues and cell lines, and observed that miR-124 expression was markedly decreased in CRC tissues and cell lines. Functional assays further revealed the inhibitory role of miR-124 in regulating the cell viability and proliferative ability of CRC. EdU assay revealed that, in the negative control (NC) small interfering RNA (siRNA) group, the average proportion of new cells incorporating EdU was 27.1%, which increased to

39.8% in miR-124 inhibitor-transfected cells. Furthermore, the proliferative capacity of SW620 cells transfected with miR-124 inhibitor declined with increasing miR-124 inhibitor concentrations (from 80 to 120 nmol/μl) and transfection times (from 24 to 48 h), which demonstrated that it suppressed the proliferation of miR-124-induced cells. High levels of miR-124 expression, on the other hand, prevented cell survival and proliferation. Similar to this, a colony-forming assay revealed that CRC cells transfected with miR-124 inhibitor had improved transformation ability compared to cells treated with negative control siRNA, whereas CRC cells overexpressing miR-124 had significantly decreased transformation ability, showing that miR-124 could prevent the invasion and migration of CRC cells (39). Taniguchi *et al* (40) found that the ectopic expression levels of miR-124 induced the apoptosis and/or the autophagy of CRC cell lines. Mechanistically, prokaryotic and eukaryotic genomes undergo DNA methylation, a post-replication alteration that plays crucial biological roles, such as controlling gene expression, deactivating the X chromosome and maintaining chromosomal integrity (91-94). miR-124 is silenced in CRC via promoter methylation, among other mechanisms that contribute to its downregulation, which was first reported by Lujambio *et al* (95), who found that CpG island hypermethylation caused miR-124 transcriptional inactivation in human malignancies. The activation of cyclin D kinase 6, a known oncogenic factor, and the phosphorylation of the tumor suppressor gene, retinoblastoma, were both shown to be causally related to the epigenetic loss of miRNA-124a (95). A previous study examined how miR-124 effectively controlled DNA hypomethylation by targeting DNA-methyltransferase (DNMT)3B and DNMT1. As a consequence of the elevated expression of miR-124, the hypermethylated and suppressed E-cadherin, methylguanine methyltransferase, and P16 genes in CRC were also re-expressed (96). The expression of polypyrimidine tract-binding protein 1 (PTBP1) may be regulated by miR-124. PTBP1 is able to alternatively splice pyruvate kinase muscle isoform 1 (PKM1) to create pyruvate kinase muscle isoform 2 (PKM2). This causes the PKM2/PKM1 ratio to increase, which prevents tumor cells from performing aerobic respiration even when oxygen levels are adequate. The proliferation of neoplastic cells may be affected by improper metabolism. Through a PTBP1/PKM1/PKM2 feedback loop, miR-124 was shown to reduce the development of CRC cells (40). Bioinformatics analysis and dual luciferase assays conducted by Zhu *et al* (97) revealed that XIST served as a ceRNA to modulate miR-124 activity and inhibit the transcriptional degradation of miR-124 targets, such as serum/glucocorticoid regulated kinase 1 (SGK1). By serving as a miR-124 sponge and therefore reducing SGK1 protein expression in DOX-resistant CRC cells, XIST knockdown reduced the ability of these cells to withstand DOX. Consequently, miR-124 may be a promising therapeutic target for enhancing the efficacy of DOX-based chemotherapy in patients with CRC (97). In terms of the impact of miR-124 on radiotherapy and drug resistance, miR-124 overexpression has been shown by Zhang *et al* (98) to increase the sensitivity of CRC cells to radiation, while knockdown of miR-124 induces cell resistance to irradiation by targeting paired related homeobox 1. The study by Xie *et al* (99) demonstrated that miR-124 directly targeted calpain 2 to enhance oxaliplatin-based chemotherapy. The clinical importance of C-X-C motif chemokine ligand 12 (CXCL12)/C-X-C chemokine receptor type 7 (CXCR7) aberrant signaling in driving EMT and invasion during CRC development was identified by Si *et al* (100). These results indicate the possibility of inhibiting CXCL12/CXCR7 aberrant signaling-induced metastasis of CRC by targeting yes-associated protein 1 nuclear translocation. In summary, these results indicate a major anticancer role of miR-124, which may serve as a fresh point of focus for the diagnosis and treatment of CRC.

HCC. Liver cancer is the sixth most prevalent solid cancer worldwide, particularly in China. There are ~841,000 new cases and 782,000 deaths associated with this disease worldwide, rendering it a serious health concern (4). HCC is the most common type of liver cancer and comprises >90% of all instances of primary liver cancer. Patients typically succumb to intrahepatic or extrahepatic metastasis in the absence of suitable therapy. Metastasis is often coupled with the development of new tumors (101,102). Consequently, further research on the metastatic mechanisms of HCC may help to elucidate HCC metastasis factors and to identify novel therapeutic targets.

RT-qPCR and immunohistochemical analysis conducted by Wang *et al* (103) revealed that miR-124 was notably downregulated in a cohort of 60 pairs of HCC tissues and Hca-F cells in contrast to nearby normal tissues and the normal hepatic cell line, NCTC1469, suggesting that miR-124 may play a critical role in regulating HCC tumorigenesis. Moreover, biological function assay demonstrated that miR-124 overexpression markedly suppressed the viability and proliferation of HepG2 cells. The results of wound healing assay indicated that the overexpression of miR-124 in HepG2 cells attenuated the wound healing process compared with the control cells. Importantly, the results of Transwell assay without Matrigel coating demonstrated that HepG2 cells expressing miR-124 migrated to the lower chamber to a lesser extent, in comparison to the control cells. Likewise, cell invasion was also observably inhibited by transfection with miR-124, as confirmed in the Transwell assay with Matrigel (104). All the aforementioned findings indicate that miR-124 functions as a tumor inhibitor in HCC. Furthermore, in HCC cell lines, miR-124 overexpression was shown to decrease the expression levels of three mesenchymal markers (fibronectin, vimentin, and N-cadherin), whereas it increased the expression levels of three epithelial indicators (E-cadherin, α-catenin and β-catenin). Additionally, immunofluorescence labeling revealed that in HCC cell lines, the expression of those three epithelial markers increased whereas the expression of the aforementioned three mesenchymal markers decreased (105). Adrenoceptor β2 and E-cadherin are directly suppressed by EZH2, which contributes to the activation of EMT (106,107). The association between EMT and the invasion and metastasis of cancer cells is widely recognized (108). Notably, miR-124 specifically targets the 3'-UTR of EZH2 to alter the synthesis of E-cadherin, according to Zheng *et al* (105), suggesting that miR-124 can control the progression of EMT. A previous study demonstrated that circHIPK3 served as a miR-124 sponge and significantly inhibited the expression level of miR-124 in HCC cells. These findings suggested that circHIPK3 may promote HCC cell proliferation and migration, whereas opposite effects

were observed upon the overexpression of miR-145, which indicated that miR-124 inhibition rescued the decrease in the proliferation and migration of HCC cell lines caused by circHIPK3 knockdown (109).

A family of transmembrane channels termed aquaporins (AQPs) transport solutes, such as glycerol and water (110,111). Previous studies have reported a critical role for AQPs in tumorigenesis and cancer progression (112,113). AQP3 has been shown to be overexpressed in HCC, and patients with elevated levels of AQP3 have a negative prognosis (114). Moreover, Chen *et al* (109) confirmed that AQP3 was a target of miR-124 and inhibited the expression of AQP3. The knockdown of circHIPK3 reduced the proliferation and migration abilities of HCC cells, which could be rescued by a miR-124 inhibitor. Furthermore, the circHIPK3-induced suppression of AQP3 expression may be reversed by miR-124 inhibition. These results demonstrated that circHIPK3 controlled the migration and proliferation of HCC cells by sponging miR-124, which in turn controlled the expression of AQP3 (109). Further research on the circHIPK3-miR-124-AQP3 axis may provide new perspectives for the future therapy of HCC. Yu *et al* (115) suggested that circHIPK3 accelerated cell proliferation and invasion by sponging miR-124. MALAT1, a lncRNA linked with lung adenocarcinoma, may promote the growth of HBx-induced malignancy (116). The 3'-UTR of miR-124 in cancer stem cells (CSCs) can specifically bind caveolin-1 (CAV1), which indicates that miR-124 can be overexpressed by targeting CAV1. Therefore, the high expression of CAV1 can inhibit the self-renewal and tumorigenesis of liver CSCs. When miR-124 is absent, this effect disappears. Other lncRNAs, such as DS cell adhesion molecule-antisense RNA 1 and miR-124 have also been found to interact in HCC (117). Taken together, these findings may provide new perspectives on the pathogenesis of HCC and may provide underlying strategies for miRNA-directed therapy. However, future studies are required to determine and elucidate the *in vivo* implications and other potential mechanisms of miR-124.

Lung cancer. Lung cancer is the leading cause of cancer-associated mortality worldwide, accounting for ~1.4 million deaths each year (118). The two main types of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) (119). NSCLC is diagnosed in ~85% of patients, while the remaining ~15% of patients are diagnosed with SCLC (120). Despite the therapeutic progress that has recently been made, the 5-year OS rates of patients with NSCLC remain low (121). Increasing evidence has indicated that cancer metastasis or recurrence is frequent in NSCLC therapy, and is mainly responsible for the low 5-year survival rate (122,123). Thus, understanding the mechanisms of NSCLC progression is critical.

miR-124 has been found to function as a regulator in lung cancer. Yang *et al* (124) demonstrated that miR-124 expression was significantly lower in 40 NSCLC tissues compared with paired non-cancerous lung tissues. Furthermore, the miR-124 expression level was strongly decreased in several NSCLC cell lines (LTEP-a-2, H226, A549, H460, 95C, 95D and H1299) compared with HBE cells. Transwell assays revealed that the A549 and H1299 cells with an elevated expression of miR-124 exhibited reduced migratory and invasive abilities. Furthermore, the A549 and H1299 cells with a downregulated expression miR-124 exhibited increased migratory and invasive abilities (124). According to a previous study, TGF-stimulation can cause A549 cells to initiate EMT, which is followed by a loss of cell-to-cell adhesion and an increase in cell mobility (125). Zu *et al* (126) demonstrated that miR-124 expression could partially induce EMT by suppressing the expression of N-cadherin and vimentin, whether it was transfected before or after TGF induction. A549 cell EMT morphology was also observed when miR-124 was transfected, and the authors of that study noted that miR-124 expression in A549 cells lowered N-cadherin and vimentin expression, but had no effect on E-cadherin expression, particularly in the absence of TGF stimulation. These data revealed that expression of miR-124 had the ability to partly reverse the EMT process (126). Previous studies have suggested that the methylation of the miR-124 promoter may reduce the production of the gene in human tumors (127,128). Moreover, Zu *et al* (126) discovered that the miR-124 promoter was hypermethylated in NSCLC cells. Additionally, 5-azacytidine therapy significantly increased the expression of miR-124 in these cells. The authors found that TGF-stimulated miR-124-1/2 promoter hypermethylation could be significantly reduced, but miR-124-3 promoter hypermethylation showed no effect. Further analysis using bisulfate sequencing and PCR revealed that TGF-β induction hypermethylated the miR-124-2 promoter but had no effect on the miR-124-3 or miR-124-1 promoter methylation (126). Moreover, A549/DDP cells have been shown to be more sensitive to cisplatin as a result of miR-124 overexpression; their apoptotic rate has been shown to increase, and their invasive and metastatic capacities have been found to be inhibited by miR-124 mimics (129). Another study revealed that miR-124 may interact with circHIPK3 to regulate the expression of miR-124 targets in lung cancer cells, including as STAT3, sphingosine kinase 1 (SphK1) and cyclin-dependent kinase 4 (CDK4). CircHIPK3 siRNA increased miR-124 expression, whereas circHIPK3 hyperexpression by LV-circHIPK3 decreased it (130). Notably, a miR-124 inhibitor significantly decreased lung cancer cell death and proliferation, as well as the downregulation of miR-124 targets caused by circHIPK3 siRNA (130). Wu *et al* (131) demonstrated that lncRNA MALAT1 could competitively regulate miR-124 after reacting with argonaute 2 to form a complex. lncRNA MALAT-1 could sponge miR-124 to regulate EMT. A decrease in the expression of miR-124 could significantly reverse the inhibition of cell proliferation, variability, invasion and migration, and EMT mediated by lncRNA MALAT1 knockdown. Li *et al* (132) found that lncRNA 1308 contributed to the sponging of miR-124, which resulted in the overexpression of a disintegrin and metalloproteinase 15 (ADAM15). The reduced expression of miR-124 and the enhanced expression of ADAM15 may clearly counteract the inhibitory effects of lncRNA 1308 knockdown on cell invasion, proliferation and migration. It was identified that the lncRNA 1308/miR-124/ADAM15 regulatory network was associated with NSCLC cell invasion and proliferation, and may promote carcinogenesis in NSCLCs; thus, it could be used to develop novel diagnostic and treatment methods for NSCLC (132). Similarly, Liu *et al* (133) reported that exosomal circRNA plasmacytoma variant translocation 1 (PVT1) derived from lung cancer mediated macrophage

polarization via the miR-124-3p/EZH2 axis to potentiate lung cancer cell proliferation, invasion and migration. These findings demonstrated that miR-124 may inhibit the ability of NSCLC cells to become malignant via an mRNA-guided mechanism. However, further research is warranted to elucidate the alternative regulatory mechanisms, as well as the therapeutic utility of miR-124 in lung cancer.

Ovarian cancer. With a high mortality rate observed over the past few decades, ovarian cancer continues to be one of the major causes of mortality among women worldwide (134-136). The primary factor behind this high mortality rate is the fact that >70% of patients are diagnosed at an advanced stage of the disease and have already developed distant tumors (137,138). According to previous studies, complex changes in the genome, particularly in the expression and function of several miRNAs, are linked to ovarian cancer (137,139). The exact mechanisms through which miRNAs are associated with the invasion and migration of ovarian cancer cells remain unclear, despite the fact that multiple studies have suggested the potential utility of miRNAs in ovarian cancer diagnosis, prognosis and therapy (140,141). Therefore, it would be crucial for clinical practice to identify effective biomarkers for ovarian cancer diagnosis and therapy.

Yuan *et al* (41) evaluated the expression of miR-124 in 30 clinical tumor samples of tissue and 30 non-neoplastic ovarian tissue, and demonstrated that compared to non-neoplastic reference tissues, the majority of ovarian cancer tissues exhibited considerably reduced expression levels of miR-124. In the study by Zhang *et al* (142), miR-124 expression was also found to be reduced in ovarian cancer cell lines. The biological effects of miR-124 on the proliferation and invasion of ovarian cancer cells were then demonstrated by various functional assays. A wound healing assay revealed that the overexpression of miR-124 mimics markedly decreased the migration of the ovarian cancer cell lines, SKOV3 and OCVAR,3 as compared to the scramble control or NC at 24 and 48 h. Furthermore, the ectopic synthesis of miR-124 considerably decreased the invasion of these cell lines in comparison to the scramble control or NC groups. miR-124 overexpression reduced the proportion of cells in the S phase, and significantly increased cell apoptosis and the proportion of OVCAR3 and SKOV3 cells in the G0/G1 phase (142). In terms of the mechanisms, Yuan *et al* (140) found that miR-124 directly suppressed the expression of PDCD6 in ovarian cancer. Notably, the expression of PDCD6 reversed the inhibition of cell migration and invasion caused by miR-124, as well as the activation of cell death (141). In the study by Zhang *et al* (142), SphK1 was shown to be a predicted target of miR-124, and miR-124 functioned as an inhibitor by directly binding to the anticipated binding location of the 3'-UTR of SphK1. SphK1 overexpression prevented cells from miR-124 from inhibiting cell migration and invasion (142). Additionally, Deng *et al* (143) demonstrated that the overexpression of miR-124-3p.1 reduced the apoptotic cell death induced by carboplatin in ovarian cancer cell lines. They established miR-124-3p.1-targeted CAV1 in ovarian cancer as the mechanism behind this effect. The overexpression of miR-124-3p.1 prevented CAV1 from being expressed, which reduced AKT activation and Bad phosphorylation. As a result, Bcl-xL function was downregulated, and carboplatin enhanced the induction of mitochondrial death (143). It has been shown that the miR-124-3p/jagged canonical Notch ligand 1 (JAG1) pathway promotes the apoptosis and inhibits the proliferation of ovarian granulosa cells (144). In conclusion, these results highlight the tumor suppressive function of miR-124, and highlight its potential as a prognostic indicator for patients. Further mechanistic studies including larger tumor samples are, however, urgently required.

Prostate cancer. The most frequent disease among males and the subsequent largest reason for cancer-related mortality is prostate cancer, with >29,000 males succumbing to prostate cancer in the USA in 2020 (145). Despite the fact that prostate cancer may be treated with cutting-edge techniques, such as androgen deprivation therapy and docetaxel chemotherapy (146,147), the survival rate of patients with prostate cancer remains low, and the 5-year survival rate is only 29% (74,148). In addition, 30% of patients relapse after receiving first treatment (149). Thus, identifying novel diagnostic biomarkers and therapeutic targets for enhancing the survival rate of patients with prostate cancer is of utmost importance.

Zhang *et al* (150) investigated miR-124 expression in 37 pairs of surgical specimens from patients with prostate cancer using RT-qPCR, and found that miR-124 expression was reduced at varying degrees in cancerous tissues. Shi *et al* (42) examined the level of miR-124 expression in prostate cancer cell lines, and found that the expression of miR-124 was lower in malignant cell lines compared with benign cell lines, Northern blot analysis was performed on these cell lines and similar results were obtained. Functionally, Transwell and cell attachment assays demonstrated that upregulation of miR-124 led to a marked reduction in the attachment to fibronectin, a vital component of the extracellular matrix, and impaired the abilities of cell migration and invasion (42). Another study suggested that upregulation of miR-124 may prevent prostate cancer cells from proliferating, indicating that miR-124 functions as a tumor inhibitor (151). It was demonstrated that the tumor inhibitor miR-124 was a critical regulator of an oncopathway in prostate cancer, modulating the expression of EZH2, Src and AR variants that contribute to the pathogenesis of the disease and resistance to treatment, and that miR-124 recovery decreased the proliferation of enzalutamide-resistant prostate cancer cells, rendering them more responsive to the drug (151). Importantly, it was found that synthetic miR-124 delivered systemically via polyethylenimine (PEI) reduced the growth of both androgen-dependent and androgen-independent prostate cancer cells as well as that of cells resistant to enzalutamide (151). Another study observed that lncRNA opioid growth factor receptor pseudogene 1 (OGFRP1) induced cell proliferation and inhibited cell apoptosis by modulating miR-124, which was expected to interact with lncRNA OGFRP1 (152). Additional analyses confirmed that miR-124 and lncRNA OGFRP1 may interact, and that miR-124 downregulation partially counteracted the stimulation of proliferation and the suppression of apoptosis caused by lncRNA OGFRP1 overexpression in prostate cancer cells (152). Taken together, these findings provide a preclinical justification for monitoring miR-124 levels in cancer treatment. However, further research is necessary to validate the

probable mechanisms and clinical significance of miR-124 in prostate cancer.

Head and neck squamous cell carcinoma (HNSCC). With ~600,000 new cases and a mortality rate of 223,000-300,000 fatalities per year, head and neck cancer is the sixth most common type of cancer worldwide (153,154). Squamous cell carcinomas, which develop in the squamous epithelial cells of the nasal cavity, paranasal sinuses, oral cavity, oropharynx, larynx and hypopharynx, account for the majority of instances of head and neck cancer (153). Currently, alcohol misuse, long-term cigarette use and human papillomavirus infection are the primary risk factors for HNSCC and are connected to age, sex and ethnicity (155). The relative frequency of these risk factors causes a variance in the distribution of HNSCC internationally. The most hazardous characteristic of HNSCC is that cancer is commonly identified at late stages (T3 or T4), when the survival rate is decreased to 20%, resulting in high mortality and morbidity rates (156,157). By contrast, the 5-year survival rate of patients is 80% if HCSCC is identified at an early stage (T1 or T2) (158,159). Therefore, including biomarkers unique to various ethnic groups holds promise for screening, early identification and tracking therapy response in HNSCC, rendering it an indispensable aspect of modern clinical practice.

Zhao *et al* (160) and Yang *et al* (161) measured the expression level of miR-124 in HNSCC tissue samples and cells. Their findings demonstrated that miR-124 expression in HNSCC tumors was markedly reduced as compared to that in surrounding healthy tissues. The expression of miR-124 in HNSCC cell lines was also significantly lower than that the in non-cancerous oral keratinocyte cell line. The downregulation of miR-124 has been implicated in tumor-promoting activities, whereas its upregulation is associated with tumor-suppressing functions in HNSCC (160,161). Zhao *et al* (160) demonstrated that the upregulation of miR-124 caused the substantial suppression of cellular proliferation *in vitro*, as well as a reduction in tumor xenograft growth in animal models. Moreover, the upregulation of miR-124 led to G1 phase cell cycle arrest, and promoted the creation of fewer and smaller colonies, thereby substantiating its role as a suppressor of tumors in HNSCC. Additionally, Zhao *et al* (160) demonstrated that miR-124 specifically bound to the complementary 3'-UTR sequence motif of SphK1 in HNSCC, inhibiting SphK1 production. Instead of using vector-transfected JHU-22 cells and tumor xenografts, miR-124 mimics were used to transfect JHU-22 cells; the results demonstrated a buildup of ceramide, higher levels of the pro-apoptotic proteins, Bax, PARP and Bad, the reduced expression of the anti-apoptotic proteins, Bcl-xL and Bcl-2, as well as the increased production of caspase proteins and cytochrome *c* (160). Yang *et al* (161) investigated the biological consequences of miR-124 in cetuximab-treated HNSCC cells. In comparison to cetuximab treatment, their study found that miR-124 overexpression dramatically decreased the viability of cells. In comparison to cetuximab therapy, the overexpression of miR-124-3p increased the apoptosis of CAL27 and SCC-9 cells by 11.23 and 9.76%, and the number of TUNEL-positive cells by 7.87 and 8.15%, respectively (161). miR-124-3p overexpression consistently enhanced the inhibitory effects of cetuximab on Bcl-2 expression and the activation of broken caspase 3 and Bax, indicating that it may improve the sensitivity of HNSCC cells to cetuximab (161). It was also revealed that lncRNA PVT1 downregulation resulted in the decreased methylation of the miR-124-3p promoter, which led to the increased expression of miR-124-3p. Functional rescue experiments revealed that the overexpression of miR-124 markedly suppressed the effects of PVT1 overexpression on apoptosis and cell proliferation. This demonstrated the functional role of miR-124-3p as a target in the control process of PVT1-mediated cetuximab chemosensitivity (161). In conclusion, these findings provide insight into the ability of miR-124 to inhibit the malignant characteristics of HNSCC cells through the modulation of mRNA and lncRNA interactions. It thus would be prudent to determine whether miR-124 expression changes according to the stage of HNSCC.

4. Potential mechanisms of miR-124 in various tumors

It is widely acknowledged that improving the patient survival rate requires an enhanced of understanding the related mechanisms and effective biomarkers for determining tumor occurrence and metastasis. Furthermore, the early detection of these aggressive cancer types during the course of the illness and the development of effective therapeutics are expected to decrease cancer mortality rates. Previous studies have demonstrated that multiple signal transduction pathways are associated with cancer occurrence and development (162-164). The aim of the present review was to summarize the associations between several regulatory systems that are involved in the initiation and development of tumors. Firstly, it was reported that miR-124 can directly influence the progression of various cancer types via several signaling pathways (Fig. 3). Adult tissue homeostasis and embryonic development have both been demonstrated to be dependent on Wnt/β-catenin signaling, which is often dysregulated in a number of malignancies (165). Classical Wnt ligands initiate Wnt/β-catenin signaling, which causes the protein complex comprised of APC, Axin and GSK3 to degrade, inhibiting β-catenin (166). Stable β-catenin moves into the nucleus to begin the process of the transcription of genes downstream, tightly regulating cell division and the development of tumors. It has been proposed that aberrant PI3K/Akt signaling exists in human cancer (167,168). Epidemiological and experimental research has established abnormal PI3K/Akt signaling pathway activation as a critical stage in the development and maintenance of human cancer. Previous research has demonstrated that PI3K/Akt triggers a signaling cascade that modulates tumor cell proliferation, invasion, metastasis and survival, in addition to affecting patient prognosis (169,170). PIK3CA is an oncogene part of the PI3K signaling pathway, and it is connected to cell proliferation and carcinogenesis in multiple tumor types (171,172). The NF-κB signaling pathway is regarded as a vital factor in numerous steps of carcinogenesis and progression (173). The critical function of the NF-B signaling system in mediating angiogenic neovascularization, EMT, and cancer cell 'stemness', as well as the mechanisms through which it contributes to chemoresistance, radioresistance and endocrine resistance, have been emphasized in previous research, which are associated with invasive phenotypes that cause early relapse, late disease stages

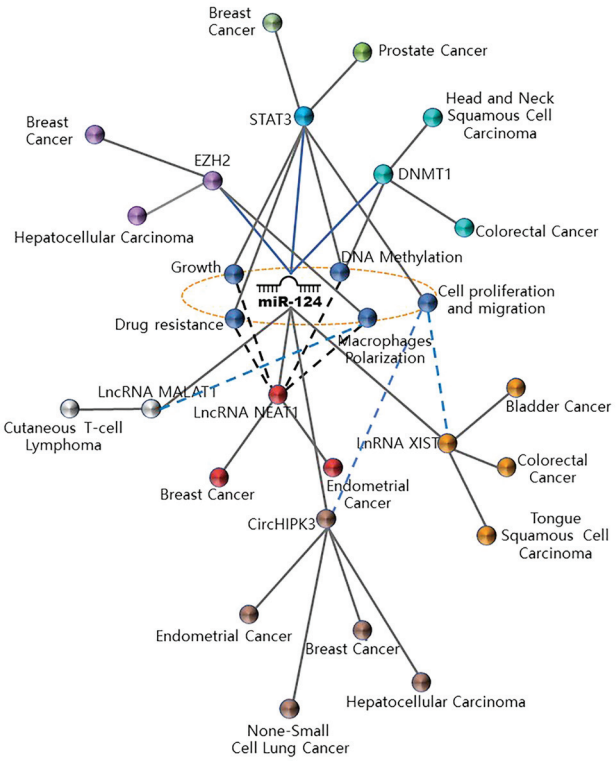

Figure 3. MicroRNA-124 regulates cancer progression through multiple signaling pathways (96,97,109,130,249-252). NEAT1, nuclear enriched abundant transcript 1; XIST, X-inactive specific transcript; DNMT1, DNA-methyltransferase 1.

and a poor OS (174,175). The JAK/STAT signaling system is a widely expressed intracellular signal transduction route that is involved in a variety of significant biological processes, including the control of immune response, cell division, apoptosis and differentiation (176). Since the overactivation of the JAK/STAT signaling system is intimately related to the development, progression, invasion and metastasis of several tumors, it is acknowledged as a novel therapeutic target for a range of cancer types (177-179). The Notch signaling system is essential for cell survival, differentiation, death and proliferation, particularly in cancer cells. Notch may become activated by connecting with the cell-bound ligands. JAG1, JAG2, DLL-1, DLL-3 and DLL-4 are known as five Notch ligands exist in mammals (180). In the usual Notch signaling pathway, a Notch ligand expressed on the cell surface interacts with a Notch receptor expressed on the surface of a neighboring cell to activate Notch signaling (181). Many recent studies have shown (as discussed below) that miRNA-124 can play an inhibitory role in the development of various tumors through the action of the aforementioned signaling pathways

CRC. It was discovered that the Wnt/β-catenin signaling pathway controls the proliferation, invasion and metastasis of CRC cells (182,183). miR-124 regulates Wnt4, a component of the Wnt/β-catenin signaling system, decreasing CRC cell proliferation *in vitro* and inhibiting tumor development *in vivo* (182). A recent study indicated that miR-124 suppresses CRC proliferation, migration and invasion by downregulating the DNMT3B and DNMT1 level (184). The inhibition of DNMT1 and DNMT3b activity has been demonstrated to regulate the expression of genes involved in the Wnt/β-catenin pathway (185). Thus, miR-124 may be involved in the Wnt/β-catenin pathway by regulating DNMT3B and DNMT1, leading to the inhibition of CRC development.

BC. It is widely recognized that the Axin family, which includes Axin1 and Axin2, regulates the amount of Wnt/β-catenin to negatively modify the Wnt/β-catenin signaling pathway, and is crucial for the development and pathophysiology of a number of human illnesses, including cancer (165,186,187). The study by Yang *et al* (62) revealed that miR-124-3p.1 targeted the 3'-UTR of Axin1 mRNA in BC cells. miR-124-3p.1 overexpression promoted cell proliferation, which was suppressed by the overexpression of Axin1 in BC cells. Therefore, utilizing miR-124-3p.1 mimics to target Wnt/β-catenin signaling pathway genes, including cyclin D1 and c-Myc prevented Axin1 from being overexpressed (62). They also found that miR-124-3p.1 mimic therapy mimicked the effects of Axin1 knockdown by upregulating β-catenin and Bcl-2, while downregulating β-catenin phosphorylation and the levels of the apoptosis-related protein, Bax. Taken together, these findings demonstrated that miR-124 regulated growth of BC by regulating Wnt/β-catenin signaling (62).

HCC. Lang and Ling (188) identified that PIK3CA played a direct role in targeting miR-124 in HCC cells, and thus contributed to marked decrease in PIK3CA at the mRNA and protein level. Notably, the overexpression of miR-124 suppressed Akt and mTOR mRNA, as well as their total and phosphorylated protein levels, suggesting that miR-124 may be a crucial modifier of the PI3K/Akt signaling pathway, thereby resulting in the suppression of proliferation and tumorgenicity of HCC cells (188). According to Cao *et al* (36), miR-124 controls the NF-κB signaling pathway, which prevents HCC from proliferating and migrating. The researchers discovered that the overexpression of miR-124 in HCC was linked to a significant decrease in the protein level of p-p65, p-nuclear factor of light polypeptide gene enhancer in B-cells inhibitor and c-Myc. By contrast, the downregulation of miR-124 suppressed the expression level of p-p65, c-Myc and p-IκBα in HCC (36). TNF receptor associated factor (TRAF6) is a critical player in the NF-κB signaling pathway, in addition to being triggered by various stimuli, such as DNA damage. The expression and activity of TRAF6 are closely controlled (189,190). A dual-luciferase reporter assay conducted by Xie *et al* (191) revealed that the upregulated expression of miR-124 markedly suppressed the activity of Firefly luciferase with the TRAF6-3'-UTR, thus inhibiting the expression of TRAF6, resulting in the inhibition of the DNA damage-activated NF-κB signaling pathway and in the enhancement of tumor chemosensitivity in HCC. The aforementioned studies on the miR-124/TRAF6/NF-κB axis illustrate that the combined targeting of the NF-κB signaling pathway may provide a possible approach for HCC therapy.

Endometrial cancer (EC). Lv *et al* (192) revealed that the overexpression of miR-124 markedly downregulated the protein levels of p-PI3K and p-AKT in endometrial cancer cells. Further evidence that the intergenic non-protein encoding RNA, regulator of reprogramming, was responsible for the activation of the PI3K/Akt signaling pathway in carcinoma of

the endometrium was provided by the considerable increase in the expression levels of these proteins when miR-124 was inhibited. Previous research has demonstrated that miR-124 controls the development of various targets in endometrial cancer. Li *et al* demonstrated that miR-124 directly targeted STAT3 or indirectly inhibited the phosphorylation of STAT6 by targeting IL-3R, thereby inhibiting the proliferation migration and invasion of EC cells (193). A recent study suggested that miR-124-3p is a downstream molecule of NEAT1 and is negatively regulated by it; thus, the silencing of NEAT1 may inhibit EC endometrial stromal cell proliferation, migration and invasion and promote apoptosis by targeting miR-124-3p (194).

GC. It has been reported that *JAG1* and *COL4A1* are direct targets of miR-124 in GC (195). Furthermore, the expression of JAG1 and the Notch signaling pathway have been found to be inhibited. By contrast, the suppression of miR-124 has been shown to lead to an increased JAG1 expression and improve Notch signaling pathway. Importantly, blocking Notch signaling results in the amplification of miR-124 expression (196). By contrast, epidermal ectopic activation of Notch signaling could repress miR-124 expression (196). Xiao *et al* (197) discovered that miR-124 suppressed the function of the Notch signaling pathway in order to target the JAG1 gene, thus suppressing the invasion, migration and proliferation of GC cells. These findings demonstrated that the miR-124/Notch axis that may have therapeutic potential in GC by functioning as a tumor inhibitor throughout the development of GC and by interacting with the Notch signaling pathway. Furthermore, Zheng *et al* (198) revealed that miR-124 overexpression suppressed the expression of p-PI3K and p-AKT in GC cells, resulting in the repression of cell proliferation and the promotion of cell apoptosis in GC.

Prostate cancer. Wu *et al* (199) demonstrated that the decreased expression of miR-124 reduced the G_0/G_1 phase ratio, inhibited cell apoptosis, and promoted the expression of STAT3, p-STAT3, cyclin D1 and Bcl-2, as well as the ratio of the S and G_2/M phases in prostate cancer. The overexpression of miR-124 attenuated clonal formation, cell invasion, the ratio of S and G_2/M phase and cell apoptosis, and also enhance the G_0/G_1 phase ratio in prostate cancer. This finding suggested that miR-124 downregulation induced the upregulation of STAT3 expression and facilitated prostate cancer initiation, while miR-124 overexpression decreased prostate cancer proliferation, invasion and resistance to apoptosis via the JAK-STAT3 signaling pathway (199). Taken together, these data suggest that miR-124 may become a novel therapeutic target and biomarker for prostate cancer in the future.

5. Underlying clinical applications of miR-124 in human cancer

The early diagnosis of cancer is a difficult task, and thus the loss of the optimal opportunity for curative surgery leads to low survival rates (88). Specific tumor biomarkers that reflect the molecular differences related to cancer, which has a great utility for early detection, are essential, and may be valuable for selecting the most effective treatment options and obtaining vital therapeutic time for patients with cancer. Prognostic indicators may be useful in clinical practice for predicting the clinical prognosis of patients with cancer who have not yet received therapy. Previous studies have shown that the expression profiles of miRNAs can predict the development of cancer or the differentiation of cancer subtypes. However, due to the uncertainty of the molecular functions of miRNAs, it is difficult to precisely predict the development of cancer. Generally, ideal and convenient biomarkers should have some typical and crucial qualities. Previous studies have revealed that miR-124 is strongly associated with a variety of biological functions in cancer cells, and may also function as a possible diagnostic biomarker and therapeutic target in human cancer in the future (46,200,201).

Bladder cancer. Patients with bladder cancer are divided into two distinct categories: One with high levels of expression and one with low levels of expression based on the average level of miR-124 expression. It has been shown that bladder cancers with lymph node metastasis (LNM) and advanced-stage cancers clinically have a lower expression of miR-124 (202). In addition, patients with bladder cancer with a low expression of miR-124 exhibit a shorter OS time than those with miR-124 overexpression (37). As shown by Xie *et al* (99), the OS has been shown to be worse in patients with a low miR-124 expression than in those with a high miR-124 expression.

CRC. Previous studies have shown that miR-124 expression is significantly downregulated in CRC compared to normal mucosa and that the downregulated expression of miR-124 is significantly associated with a poorer prognosis (98). Chen *et al* (96) suggested that miR-124 may be a valuable marker for CRC prognosis. According to Gao *et al* (203), the pri-miR-124 rs531564 polymorphism was significantly linked to a lower incidence of CRC. They demonstrated a strong correlation between differentiation status and LNM in patients with CRC and the pri-miR-124 rs531564 polymorphism.

HCC. Long *et al* (204) evaluated the level of miR-124 expression in HCC samples and cell lines. Their results revealed that HCC samples and cell lines had a downregulated expression of miR-124. The number of foci and tumor width were higher in individuals with a lower expression of miR-124, according to the authors' investigation into the association between the expression of miR-124 and the clinicopathological characteristics of patients with HCC. Furthermore, Kaplan-Meier survival analysis observed that decreased miR-124 expression was notably associated with shorter a DFS and OS. Cox regression analysis demonstrated that a downregulated expression of miR-124 was associated with a poor prognosis (204). The results of a Cox regression model employing multivariate analysis revealed that the findings for the prognosis of reduced expression, clinicopathological features (tumor length 5 centimeters), or amount of lesions (plural) were worse than those from univariate analysis (204). A low miR-124 expression and a high tumor size (5 cm) have also been linked to a reduction in OS and DFS (204). This proved that a key therapeutic approach for the care of patients with late-stage HCC may include producing larger amounts of miR-124 in cells. Another potential new and significant tumor marker is miR-124.

Osteosarcoma. Cong *et al* (205) detected the expression of blood miR-124 in 114 individuals suffering from osteosarcoma, 40 individuals with periostitis and 50 normal controls; they found that patients with the tumor had substantially lower levels of miR-124 expression than patients with periostitis and normal controls. Furthermore, a receiver operating characteristic curve analysis with an area under the curve of 0.846 suggested that blood miR-124 levels may serve as an underlying biomarker for separating patients with osteosarcoma from healthy controls. In addition, the specificity and sensitivity were 86.0 and 79.8%, respectively. The expression level of serum miR-124 was highly associated with clinical stage and distant metastasis, whereas it was not associated with age, sex, tumor site, tumor diameter or tumor grade (205). Patients with stage III disease had considerably lower serum levels of miR-124 than those with stage II disease. Similar to this, blood miR-124 levels were noticeably lower in patients with positive distant metastasis than they were in individuals without metastasis. According to the results of Kaplan-Meier analysis and the log-rank test, individuals with osteosarcoma who had a high serum expression of miR-124 had substantially longer survival times than those who had a low miR-124 expression. Individuals with osteosarcoma in the low blood miR-124 expression group had a poorer DFS compared to those in the high serum miR-124 expression group. Multivariate Cox proportional hazards model analysis identified that clinical stage, distant metastasis and expression of serum miR-124 were independent prognostic factors for OS and DFS (205). In summary, the aforementioned data demonstrated that miR-124 may be utilized as a diagnostic and prognostic biomarker for osteosarcoma.

Glioma. The majority of human malignant central nervous system tumors are gliomas (3). Almost 20,000 new glioma cases are diagnosed in the USA each year (206). Chen *et al* (207) revealed that the miR-124 expression level was considerably reduced in glioma tissues. Moreover, the miR-124 expression level in glioma tissues from high-grade tumors (grade III and IV) was much lower than that of glioma tissues from low-grade tumors (grade I and II). In addition, the miR-124 expression level exhibited a positive correlation with the Karnofsky performance scale scores of glioma tissues. Kaplan-Meier analysis and the log-rank test demonstrated that the OS and progression-free survival of patients with glioma with a low expression of miR-124 was markedly shorter than those of patients with miR-124 overexpression. The results of univariate and multivariate analyses revealed that the downregulated expression of miR-124 and an advanced histological grade were independent prognostic parameters that indicated a worse prognosis for patients with glioma (207). Thus, these findings indicated that miR-124 expression played a critical role in the progression of tumors; thus, it may be applied as a novel potential biomarker for evaluating clinical prognosis. At present, the greatest obstacles to cancer treatment are a delay in diagnosis, recurrence and metastasis.

Thus, finding ideal cancer biomarkers is crucial to improving the early diagnosis rate. The aforementioned findings indicate that miR-124 may be used as a potential marker for the diagnosis of multiple cancer types. However, the precise molecular mechanisms by which miR-124 functions in several types of cancer remain unclear. Therefore, the function of miR-124 in cancer needs to be further investigated and confirmed, particularly in clinical applications.

Since miRNAs can inhibit tumor development through a variety of mechanisms, the notion of treating tumors through miRNAs was born (164,208-212). In addition to its role in diagnosis and prognosis as a potential marker for cancer, miR-124 can make tumors more sensitive to treatment through different targets, thereby improving patient survival. For example, miR-124 can reverse radioresistance in esophageal cancer radiotherapy by targeting CDK4 to increase cancer cell sensitivity to radiation, and also plays a role in immunotherapy (213,214). It has been demonstrated that miR-124 not only reverses the resistance of BC stem cells to DOX by targeting STAT3 to control the hypoxia-inducible factor-1 signaling pathway (67), but also increases the sensitivity of BC cells to adriamycin by reducing DNA strand-break repair (215). A previous study inferred that miR-124 inhibited the expression of EphA2, which was beneficial for attenuating K-RAS mutation-mediated resistance to erlotinib in pancreatic cancer (216). In retinoblastoma, the miR-124/c-Myc axis exerts an oncogenic effect on disease progression, suggesting that miR-124 may be a promising therapeutic target (217). A previous study demonstrated that bio-carrier neural stem cell-derived exosomes (NSC-EXOs) loaded with miR-124-3p suppressed glioma growth via the EXO-miR-124-3p/FLOT2/AKT1 pathway, thus providing a possible measure for glioma treatment (218). miR-124 should be explored for the reversal of drug resistance in tumor treatments in the future.

6. Future prospects

The development of several innovative therapeutic strategies may result from a better knowledge of miR-124's function in the treatment of cancer. Hence, further studies on miRNA are required. According to previous research, in BC, bladder cancer, HCC, CRC, and lung, ovarian and prostate cancer cell lines, miR-124 expression is downregulated. In addition, miR-124 can prevent certain cancer cell types from migrating and proliferating. Furthermore, an abnormal miR-124 expression in cancer has been reported to be significantly associated with diagnosis, prognosis, tumorigenesis and metastasis via signaling pathways. Various studies have confirmed that miR-124 may be a potential target for cancer diagnosis and may function as a novel cancer therapeutic target or biomarker. Nevertheless, the clinical usefulness of miR-124 remains unknown, and the understanding of its biological functions is only partial. Consequently, further research on miRNAs is required (Fig. 4).

Extracellular vesicles (EVs) refers to a group of organelles with lipid bilayer membranes that are released from cells into the environment (219). It has been reported that a number of cargos are transferred across cells via EVs (191,193). More importantly, the cells of origin can be affected by the cargo of EVs. Previous studies have suggested that, compared with parental cells, exosomes carry different types of RNA (220-222). Unprotected ncRNAs in the blood are known to be susceptible to degradation by blood RNases. Nevertheless, EVs prevent the degradation of ncRNAs,

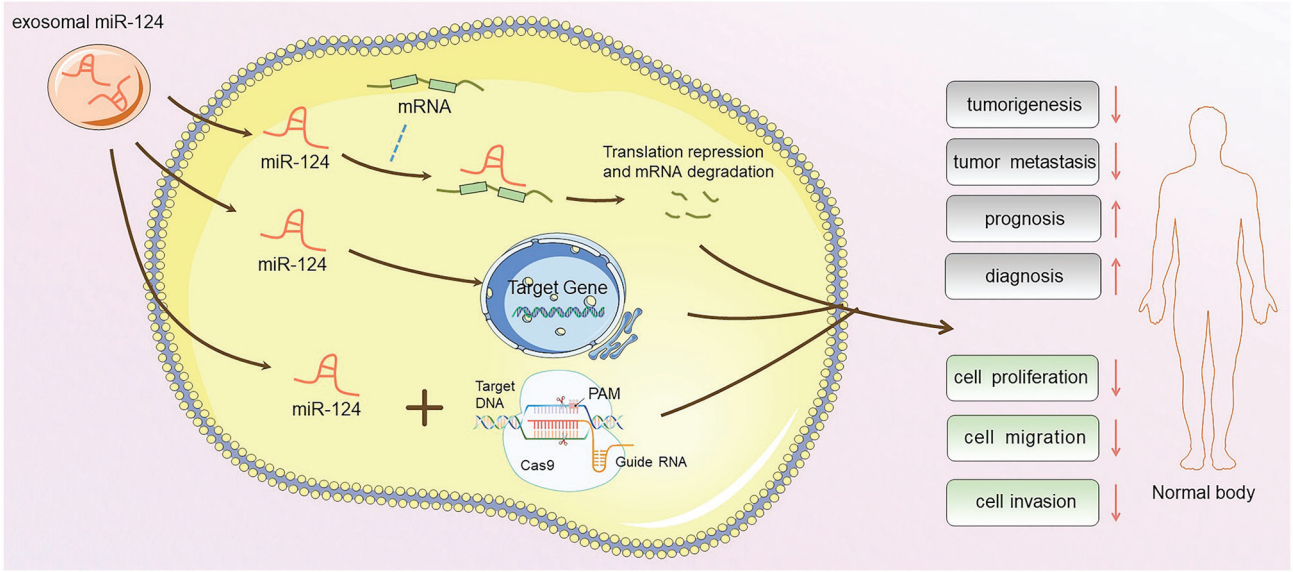

Figure 4. Future application prospects of miR-124. miR-124 can enter the cell through exosomes and can target the mRNA transcribed by oncogenes, resulting in its translation repression and degradation. Moreover, it can also act as the guiding RNA of CRISPR-Cas9, directly cut and knock out oncogenes. Both pathways can be therapeutic for cancer (245,253). miR, microRNA. Some of the elements in the figure were derived from *Servier Medical Art* (Web site: *https://smart.servier.com/*) and publication permission was obtained.

and therefore maintain their activity and integrity in the circulation. miRNAs are considered to be gene expression regulators, since they can bind to mRNAs directly and subsequently suppress the translation or degradation of target mRNAs, thus inhibiting the progression and development of tumors (223,224). It has been suggested that EV-miRNAs establish a bridge between the tumor microenvironment and cancer cells, meaning that EV-miRNAs play vital roles in both the tumor microenvironment and cancer cells (225). miRNAs are carefully packaged in EVs and sent to nearby or distant recipient cells in order to modify their gene expression. For example, in various solid cancer types, the let-7 miRNA family is secreted via EVs and is downregulated (226), which also functioned as targeting oncogenes, including high mobility group A2 and RAS (227), and tumor suppressor genes. Metastatic GC cells can reduce their intracellular antitumor ability to maintain their invasive and tumorigenic behavior, which is achieved by EVs secreting the tumor suppressor let-7 miRNA into the extracellular space (226). Kanlikilicer *et al* (228) demonstrated that ovarian cancer cells released the EV-miRNA miR-6126, which enhanced their capacity to metastasize by directly targeting integrin-1, a crucial regulator of cancer cell metastasis. It has also been shown that EVs produced by CRC promote immune escape via the upregulation of PD-L1 in TAMs, and by inducing macrophage M2 polarization via miR-21-5p and miR-200a, suggesting that EVs and miRNAs may serve as novel targets for CRC immunotherapy (229). In addition, in prostate cancer, miRNAs have been shown to inhibit the production of EVs by targeting genes associated with EV secretion, thereby mediating tumor suppression, which has led to new hypotheses for prostate cancer treatment (230). Overall, these findings demonstrated that EV-miRNAs can serve as miRNAs with either oncogenic or tumor suppressor roles, and that understanding these mechanisms may help to develop new systems that regulate the sorting of EV-miRNAs to reduce their effects on the development of cancer. It may be helpful to identify and alter the composition of cancer EVs to develop novel diagnostic, preventative and therapeutic strategies with perhaps less intrusive techniques. As such, miR-124 appears to pay a vital role in cancer diagnosis, prevention and treatment, and its expression level can be upregulated by the administration of exosomal miR-124.

As a versatile editing tool, clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9-mediated genome editing technology has attracted extensive attention worldwide (231-233). Single guide RNA (sgRNA) and DNA endonuclease Cas9 form the CRISPR-Cas9 system, and Cas9 and sgRNA conduct site-specific cleavage of double stranded DNA by guiding Cas9 to a specific DNA sequence (234). It has been demonstrated that CRISPR-Cas9 is promising for cancer treatment (235). For instance, CRISPR-Cas9-mediated CD133 deletion can prevent colon cancer invasion by lowering EMT as a possible CSC marker (236). Notably, Zhou *et al* (237) used the CRISPR/Cas9 method to successfully knockdown miR-3188 in an HCC cell line. As it efficiently inhibited the proliferation, invasion and migration of nude mice cells, as well as the development of xenograft tumors, it was observed that the CRISPR/Cas9 system played a key role in the editing and control of miRNA-related genomes. It has been shown that miR-124 downregulation inhibits tumor invasion and migration (238), suggesting that, in the future, CRISPR-Cas9 may be used to downregulate miR-124 and thus control tumor development. Moreover, due to its precision, effectiveness, simplicity and adaptability, CRISPR/Cas9, as an effective genomic engineering tool, has played a vital role in treating various diseases (239). For example, Huo *et al* (240) disrupted the precursor miRNA sequence using CRISPR/Cas9, and ovarian cancer cell invasion, migration and proliferation were decreased once

miR-21 expression was suppressed. The efficacy of cancer therapy is increased by the use of CRISPR/Cas9 gene editing technologies. To better elucidate the function of miR-124 and related therapeutic interventions, the authors aim to use CRISPR technology for miR-124 editing in future studies, with the aim of reducing the delivery failure rate of the CRISPR/Cas system in cancer cells through the combination of components.

7. Conclusion

The present review had certain strengths and limitations. The present review described current research on miR-R124 in various tumors. By summarizing these studies, the targets of action of miR-124 that are currently being studied were discussed. In addition to this, the current regulatory mechanisms of miR-124 in tumors were elaborated in-depth, and found the five most studied pathways (as described above) were summarized. Finally, by summarizing the current and future clinical applications of miR-124, it can be concluded that miR-124 is expected to be a potential marker and target for adjuvant therapy in cancer. However, due to the limited information available from miR-124 studies in tumors, many of which are still in the preliminary stage, further studies are required in the future.

miRNAs may have an impact on the etiology of malignancies. miRNAs inhibit the expression of tumor suppressors and oncogenes (241). miR-124 is abnormally expressed in various malignant tumors, including HCC, BC, NSCLC, CRC and bladder, ovarian and prostate cancer. The miR-124 expression level was confirmed to be similar in various cancer types. Furthermore, previous research (as discussed above) has revealed that miR-124 is linked to OS, LNM, DFS, clinical stage and distant metastasis, and can function as a tumor suppressor. The growth, migration, spread and death of the aforementioned cancer types may be controlled by miR-124. The characterization of specific alterations of miR-124 expression in cancer has potential for identifying biomarkers for cancer detection in the early stages, and for therapeutic intervention during cancer treatment. Previous studies have shown that miR-124 can control molecular pathways, such as the JAK/STAT signaling pathway, which is associated with tumor growth and development.

In conclusion, the present review addresses the mechanisms through which miR-124 controls cancer cell migration, proliferation, invasion and death by inhibiting the expression of oncogenic mRNAs, as well as the importance of miR-124 and its target genes in diverse malignancies. However, further investigations are required to elucidate the molecular mechanisms of miR-124 in additional human malignancies.

Acknowledgements

Not applicable.

Funding

The present study was supported by Scientific Research Projects at the Affiliated Bozhou Hospital of Anhui Medical University (By202111).

Availability of data and materials

Not applicable.

Authors' contributions

YL, YY and XW drafted the manuscript. BL, SY, YZ and MF revised the manuscript. ZF, CS, YH and BC reviewed and modified the manuscript. QZ put forward constructive opinions on the topic selection of the article. All authors have read and approved the final version. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have competing interests.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global cancer statistics, 2012. CA Cancer J Clin 65: 87-108, 2015.
2. Zaimy MA, Saffarzadeh N, Mohammadi A, Pourghadamyari H, Izadi P, Sarli A, Moghaddam LK, Paschepari SR, Azizi H, Torkamandi S and Tavakkoly-Bazzaz J: New methods in the diagnosis of cancer and gene therapy of cancer based on nanoparticles. Cancer Gene Ther 24: 233-243, 2017.
3. Vineis P and Wild CP: Global cancer patterns: Causes and prevention. Lancet 383: 549-557, 2014.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68: 394-424, 2018.
5. Basuroy R, Bouvier C, Ramage JK, Sissons M, Kent A and Srirajaskanthan R: Presenting Symptoms and Delay in Diagnosis of Gastrointestinal and Pancreatic Neuroendocrine Tumours. Neuroendocrinology 107: 42-49, 2018.
6. Koo MM, Hamilton W, Walter FM, Rubin GP and Lyratzopoulos G: Symptom signatures and diagnostic timeliness in cancer patients: A review of current evidence. Neoplasia 20: 165-174, 2018.
7. Smith JS, Lindsay L, Hoots B, Keys J, Franceschi S, Winer R and Clifford GM: Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: A meta-analysis update. Int J Cancer 121: 621-632, 2007.
8. Yan L, Xu F and Dai CL: Relationship between epithelial-to-mesenchymal transition and the inflammatory microenvironment of hepatocellular carcinoma. J Exp Clin Cancer Res 37: 203, 2018.
9. Torre LA, Siegel RL, Ward EM and Jemal A: Global cancer incidence and mortality rates and trends-an update. Cancer Epidemiol Biomarkers Prev 25: 16-27, 2016.
10. Roy PS and Saikia BJ: Cancer and cure: A critical analysis. Indian J Cancer 53: 441-442, 2016.
11. Wang JJ, Lei KF and Han F: Tumor microenvironment: Recent advances in various cancer treatments. Eur Rev Med Pharmacol Sci 22: 3855-3864, 2018.
12. Okamoto A, Watanabe T, Kamata K, Minaga K and Kudo M: Recent updates on the relationship between cancer and autoimmune pancreatitis. Intern Med 58: 1533-1539, 2019.
13. Lujambio A and Lowe SW: The microcosmos of cancer. Nature 482: 347-355.

14. Lee RC, Feinbaum RL and Ambros V: The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 75: 843-854, 1993.
15. Asli NS, Pitulescu ME and Kessel M: MicroRNAs in organogenesis and disease. Curr Mol Med 8: 698-710, 2008.
16. Bueno MJ, Perez de Castro I and Malumbres M: Control of cell proliferation pathways by microRNAs. Cell Cycle 7: 3143-3148, 2008.
17. Lu LF and Liston A: MicroRNA in the immune system, microRNA as an immune system. Immunology 127: 291-298, 2009.
18. Maatouk D and Harfe B: MicroRNAs in development. ScientificWorldJournal 6: 1828-1840, 2006.
19. Wang Y and Lee CG: MicroRNA and cancer-focus on apoptosis. J Cell Mol Med 13: 12-23, 2009.
20. Wu SG, Huang YJ, Bao B, Wu LM, Dong J, Liu XH, Li ZH, Wang XY, Wang L, Chen BJ and Chen W: miR-508-5p acts as an anti-oncogene by targeting MESDC1 in hepatocellular carcinoma. Neoplasma 64: 40-47, 2017.
21. Gao W, Li W, Xiao T, Liu XS and Kaelin WG Jr: Inactivation of the PBRM1 tumor suppressor gene amplifies the HIF-response in VHL-/-clear cell renal carcinoma. Proc Natl Acad Sci USA 114: 1027-1032, 2017.
22. Xiao X, Tang C, Xiao S, Fu C and Yu P: Enhancement of proliferation and invasion by MicroRNA-590-5p via targeting PBRM1 in clear cell renal carcinoma cells. Oncol Res 20: 537-544, 2013.
23. Wan HY, Li QQ, Zhang Y, Tian W, Li YN, Liu M, Li X and Tang H: MiR-124 represses vasculogenic mimicry and cell motility by targeting amotL1 in cervical cancer cells. Cancer Lett 355: 148-158, 2014.
24. Peng XH, Huang HR, Lu J, Liu X, Zhao FP, Zhang B, Lin SX, Wang L, Chen HH, Xu X, *et al*: MiR-124 suppresses tumor growth and metastasis by targeting Foxq1 in nasopharyngeal carcinoma. Mol Cancer 13: 186, 2014.
25. Liang YJ, Wang QY, Zhou CX, Yin QQ, He M, Yu XT, Cao DX, Chen GQ, He JR and Zhao Q: MiR-124 targets Slug to regulate epithelial-mesenchymal transition and metastasis of breast cancer. Carcinogenesis 34: 713-722, 2013.
26. Yan G, Li Y, Zhan L, Sun S, Yuan J, Wang T, Yin Y, Dai Z, Zhu Y, Jiang Z, *et al*: Decreased miR-124-3p promoted breast cancer proliferation and metastasis by targeting MGAT5. Am J Cancer Res 9: 585-596, 2019.
27. Lagos-Quintana M, Rauhut R, Yalcin A, Meyer J, Lendeckel W and Tuschl T: Identification of tissue-specific microRNAs from mouse. Curr Biol 12: 735-739, 2002.
28. Clark AM, Goldstein LD, Tevlin M, Tavare S, Shaham S and Miska EA: The microRNA miR-124 controls gene expression in the sensory nervous system of Caenorhabditis elegans. Nucleic Acids Res 38: 3780-3793, 2010.
29. Zhou Q, Long L, Shi G, Zhang J, Wu T and Zhou B: Research of the methylation status of miR-124a gene promoter among rheumatoid arthritis patients. Clin Dev Immunol 2013: 524204, 2013.
30. Ben Gacem R, Ben Abdelkrim O, Ziadi S, Ben Dhiab M and Trimeche M: Methylation of miR-124a-1, miR-124a-2, and miR-124a-3 genes correlates with aggressive and advanced breast cancer disease. Tumour Biol 35: 4047-4056, 2014.
31. Ando T, Yoshida T, Enomoto S, Asada K, Tatematsu M, Ichinose M, Sugiyama T and Ushijima T: DNA methylation of microRNA genes in gastric mucosae of gastric cancer patients: Its possible involvement in the formation of epigenetic field defect. Int J Cancer 124: 2367-2374, 2009.
32. Gao C, Shen J, Meng ZX and He XF: Sevoflurane Inhibits Glioma cells proliferation and metastasis through miRNA-124-3p/ROCK1 axis. Pathol Oncol Res 26: 947-954, 2020.
33. Zhang TH, Liang LZ, Liu XL, Wu JN, Su K, Chen JY, Zheng QY, Huang HZ and Liao GQ: [Retracted] Long non-coding RNA MALAT1 interacts with miR-124 and modulates tongue cancer growth by targeting JAG1. Oncol Rep 40: 3112, 2018.
34. Wang D, Zhang H, Li M, Frid MG, Flockton AR, McKeon BA, Yeager ME, Fini MA, Morrell NW, Pullamsetti SS, *et al*: MicroRNA-124 controls the proliferative, migratory, and inflammatory phenotype of pulmonary vascular fibroblasts. Circ Res 114: 67-78, 2014.
35. Furuta M, Kozaki KI, Tanaka S, Arii S, Imoto I and Inazawa J: miR-124 and miR-203 are epigenetically silenced tumor-suppressive microRNAs in hepatocellular carcinoma. Carcinogenesis 31: 766-776, 2010.
36. Cao J, Qiu J, Wang X, Lu Z, Wang D, Feng H, Li X, Liu Q, Pan H, Han X, *et al*: Identification of microRNA-124 in regulation of Hepatocellular carcinoma through BIRC3 and the NF-κB pathway. J Cancer 9: 3006-3015, 2018.
37. Zhou W, He L, Dai Y, Zhang Y, Wang J and Liu B: MicroRNA-124 inhibits cell proliferation, invasion and migration by targeting CAV1 in bladder cancer. Exp Ther Med 16: 2811-2820, 2018.
38. Zo RB and Long Z: MiR-124-3p suppresses bladder cancer by targeting DNA methyltransferase 3B. J Cell Physiol 234: 464-474, 2018.
39. Zhou L, Xu Z, Ren X, Chen K and Xin S: MicroRNA-124 (MiR-124) inhibits cell proliferation, metastasis and invasion in colorectal cancer by downregulating Rho-associated protein kinase 1(ROCK1). Cell Physiol Biochem 38: 1785-1795, 2016.
40. Taniguchi K, Sugito N, Kumazaki M, Shinohara H, Yamada N, Nakagawa Y, Ito Y, Otsuki Y, Uno B, Uchiyama K and Akao Y: MicroRNA-124 inhibits cancer cell growth through PTB1/PKM1/PKM2 feedback cascade in colorectal cancer. Cancer Lett 363: 17-27, 2015.
41. Yuan L, Li S, Zhou Q, Wang D, Zou D, Shu J and Huang Y: MiR-124 inhibits invasion and induces apoptosis of ovarian cancer cells by targeting programmed cell death 6. Oncol Lett 14: 7311-7317, 2017.
42. Shi XB, Xue L, Ma AH, Tepper CG, Gandour-Edwards R, Kung HJ and deVere White RW: Tumor suppressive miR-124 targets androgen receptor and inhibits proliferation of prostate cancer cells. Oncogene 32: 4130-4138, 2013.
43. Gan H, Liu H, Zhang H, Li Y, Xu X, Xu X and Xu J: SHh-Gli1 signaling pathway promotes cell survival by mediating baculoviral IAP repeat-containing 3 (BIRC3) gene in pancreatic cancer cells. Tumour Biol 37: 9943-9950, 2016.
44. Smolewski P and Robak T: Inhibitors of apoptosis proteins (IAPs) as potential molecular targets for therapy of hematological malignancies. Curr Mol Med 11: 633-649, 2011.
45. Frazzi R: BIRC3 and BIRC5: Multi-faceted inhibitors in cancer. Cell Biosci 11: 8, 2021.
46. Jia X, Wang X, Guo X, Ji J, Lou G, Zhao J, Zhou W, Guo M, Zhang M, Li C, *et al*: MicroRNA-124: An emerging therapeutic target in cancer. Cancer Med 8: 5638-5650, 2019.
47. Tutar Y: miRNA and cancer; computational and experimental approaches. Curr Pharm Biotechnol 15: 429, 2014.
48. Zhang L, Chen X, Liu B and Han J: MicroRNA-124-3p directly targets PDCD6 to inhibit metastasis in breast cancer. Oncol Lett 15: 984-990, 2018.
49. Wu Q, Xu L, Wang C, Fan W, Yan H and Li Q: MicroRNA-124-3p represses cell growth and cell motility by targeting EphA2 in glioma. Biochem Biophys Res Commun 503: 2436-2442, 2018.
50. Yu B, Jiang K and Zhang J: MicroRNA-124 suppresses growth and aggressiveness of osteosarcoma and inhibits TGF-beta-mediated AKT/GSK-3beta/SNAIL-1 signaling. Mol Med Rep 17: 6736-6744, 2018.
51. Moghadasi M, Alivand M, Fardi M, Moghadam KS and Solali S: Emerging molecular functions of microRNA-124: Cancer pathology and therapeutic implications. Pathol Res Pract 216: 152827, 2020.
52. Wang P, Zhang LD, Sun MC, Gu WD and Geng HZ: Over-expression of mir-124 inhibits MMP-9 expression and decreases invasion of renal cell carcinoma cells. Eur Rev Med Pharmacol Sci 22: 6308-6314, 2018.
53. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136: E359-E386, 2015.
54. Hosseinahli N, Aghapour M, Duijf PHG and Baradaran B: Treating cancer with microRNA replacement therapy: A literature review. J Cell Physiol 233: 5574-5588, 2018.
55. Nagini S: Breast cancer: Current molecular therapeutic targets and new players. Anticancer Agents Med Chem 17: 152-163, 2017.
56. Chen WY: Exogenous and endogenous hormones and breast cancer. Best Pract Res Clin Endocrinol Metab 22: 573-585, 2008.
57. Roodman GD: Mechanisms of bone metastasis. N Engl J Med 350: 1655-1664, 2004.
58. Scully OJ, Bay BH, Yip G and Yu Y: Breast cancer metastasis. Cancer Genomics Proteomics 9: 311-320, 2012.
59. Li Z and Kang Y: Emerging therapeutic targets in metastatic progression: A focus on breast cancer. Pharmacol Ther 161: 79-96, 2016.

60. Cai WL, Huang WD, Li B, Chen TR, Li ZX, Zhao CL, Li HY, Wu YM, Yan WJ and Xiao JR: microRNA-124 inhibits bone metastasis of breast cancer by repressing Interleukin-11. Mol Cancer 17: 9, 2018.
61. Feng T, Shao F, Wu Q, Zhang X, Xu D, Qian K, Xie Y, Wang S, Xu N, Wang Y and Qi C: miR-124 downregulation leads to breast cancer progression via LncRNA-MALAT1 regulation and CDK4/E2F1 signal activation. Oncotarget 7: 16205-16216, 2016.
62. Yang W, Cui G, Ding M, Yang M and Dai D: MicroRNA-124-3p.1 promotes cell proliferation through Axin1-dependent Wnt signaling pathway and predicts a poor prognosis of triple-negative breast cancer. J Clin Lab Anal 34: e23266, 2020.
63. Ji H, Sang M, Liu F, Ai N and Geng C: miR-124 regulates EMT based on ZEB2 target to inhibit invasion and metastasis in triple-negative breast cancer. Pathol Res Pract 215: 697-704, 2019.
64. Shi P, Chen C, Li X, Wei Z, Liu Z and Liu Y: MicroRNA-124 suppresses cell proliferation and invasion of triple negative breast cancer cells by targeting STAT3. Mol Med Rep 19: 3667-3675, 2019.
65. Sun Y, Li Q, Gui H, Xu DP, Yang YL, Su DF and Liu X: MicroRNA-124 mediates the cholinergic anti-inflammatory action through inhibiting the production of pro-inflammatory cytokines. Cell Res 23: 1270-1283, 2013.
66. Zhang Y, Li X, Zhang J and Liang H: Natural killer T cell cytotoxic activity in cervical cancer is facilitated by the LINC00240/microRNA-124-3p/STAT3/MICA axis. Cancer Lett 474: 63-73, 2020.
67. Liu C, Xing H, Guo C, Yang Z, Wang Y and Wang Y: MiR-124 reversed the doxorubicin resistance of breast cancer stem cells through STAT3/HIF-1 signaling pathways. Cell Cycle 18: 2215-2227, 2019.
68. Yu X, Li Z, Zheng H, Chan MT and Wu WK: NEAT1: A novel cancer-related long non-coding RNA. Cell Prolif 50: e12329, 2017.
69. Jiang X, Zhou Y, Sun AJ and Xue JL: NEAT1 contributes to breast cancer progression through modulating miR-448 and ZEB1. J Cell Physiol 233: 8558-5866, 2018.
70. Pang Y, Wu J, Li X, Wang C, Wang M, Liu J and Yang G: NEAT1/miR-124/STAT3 feedback loop promotes breast cancer progression. Int J Oncol 55: 745-754, 2019.
71. Shi P, Liu Y, Yang H and Hu B: Breast cancer derived exosomes promoted angiogenesis of endothelial cells in microenvironment via circHIPK3/miR-124-3p/MTDH axis. Cell Signal 95: 110338, 2022.
72. Wang YF, Yu L, Hu ZL, Fang YF, Shen YY, Song MF and Chen Y: Regulation of CCL2 by EZH2 affects tumor-associated macrophages polarization and infiltration in breast cancer. Cell Death Dis 13: 748, 2022.
73. Guo Q, Wang H, Duan J, Luo W, Zhao R, Shen Y, Wang B, Tao S, Sun Y, Ye Q, *et al*: An alternatively spliced p62 isoform confers resistance to chemotherapy in breast cancer. Cancer Res 82: 4001-4015, 2022.
74. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2016. CA Cancer J Clin 66: 7-30, 2016.
75. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, Stein KD, Alteri R and Jemal A: Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 66: 271-289, 2016.
76. Palmbos PL, Wang L, Yang H, Wang Y, Leflein J, Ahmet ML, Wilkinson JE, Kumar-Sinha C, Ney GM, Tomlins SA, *et al*: ATDC/TRIM29 drives invasive bladder cancer formation through miRNA-mediated and epigenetic mechanisms. Cancer Res 75: 5155-5166, 2015.
77. Mitin T, Hunt D, Shipley WU, Kaufman DS, Uzzo R, Wu CL, Buyyounouski MK, Sandler H and Zietman AL: Transurethral surgery and twice-daily radiation plus paclitaxel-cisplatin or fluorouracil-cisplatin with selective bladder preservation and adjuvant chemotherapy for patients with muscle invasive bladder cancer (RTOG 0233): A randomised multicentre phase 2 trial. Lancet Oncol 14: 863-872, 2013.
78. Girardi DM, Ghatalia P, Singh P, Iyer G, Sridhar SS and Apolo AB: Systemic therapy in bladder preservation. Urol Oncol 41: 39-47, 2023.
79. Ma Y, Hu Q, Luo W, Pratt RN, Glenn ST, Liu S, Trump DL and Johnson CS: 1α,25(OH)2D3 differentially regulates miRNA expression in human bladder cancer cells. J Steroid Biochem Mol Biol 148: 166-171, 2015.
80. Wang S, Wu G, Han Y, Song P, Chen J, Wu Y, Yang J and Liang P: miR-124 regulates STAT3-mediated cell proliferation, migration and apoptosis in bladder cancer. Oncol Lett 16: 5875-5881, 2018.
81. Li T, Kang G, Wang T and Huang H: Tumor angiogenesis and anti-angiogenic gene therapy for cancer. Oncol Lett 16: 687-702, 2018.
82. Annese T, Tamma R, Ruggieri S and Ribatti D: Erythropoietin in tumor angiogenesis. Exp Cell Res 374: 266-273, 2019.
83. Wang X, Wu Q, Xu B, Wang P, Fan W, Cai Y, Gu X and Meng F: MiR-124 exerts tumor suppressive functions on the cell proliferation, motility and angiogenesis of bladder cancer by fine-tuning UHRF1. FEBS J 282: 4376-4388, 2015.
84. Yao Y, Ma J, Xue Y, Wang P, Li Z, Liu J, Chen L, Xi Z, Teng H, Wang Z, *et al*: Knockdown of long non-coding RNA XIST exerts tumor-suppressive functions in human glioblastoma stem cells by up-regulating miR-152. Cancer Lett 359: 75-86, 2015.
85. Xiong Y, Wang L, Li Y, Chen M, He W and Qi L: The long non-coding RNA XIST interacted with MiR-124 to modulate bladder cancer growth, invasion and migration by targeting androgen receptor (AR). Cell Physiol Biochem 43: 405-418, 2017.
86. Lombard AP and Mudryj M: The emerging role of the androgen receptor in bladder cancer. Endocr Relat Cancer 22: R265-R277, 2015.
87. Aguiar Junior S, Oliveira MM, Silva D, Mello CAL, Calsavara VF and Curado MP: Survival of patients with colorectal cancer in a cancer center. Arq Gastroenterol 57: 172-177, 2020.
88. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, Cercek A, Smith RA and Jemal A: Colorectal cancer statistics, 2020. CA Cancer J Clin 70: 145-164, 2020.
89. Villeger R, Lopes A, Veziant J, Gagniere J, Barnich N, Billard E, Boucher D and Bonnet M: Microbial markers in colorectal cancer detection and/or prognosis. World J Gastroenterol 24: 2327-2347, 2018.
90. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A and Jemal A: Colorectal cancer statistics, 2017. CA Cancer J Clin 67: 177-193, 2017.
91. Kass SU, Pruss D and Wolffe AP: How does DNA methylation repress transcription? Trends Genet 13: 444-449, 1997.
92. Nakao M and Sasaki H: Genomic imprinting: Significance in development and diseases and the molecular mechanisms. J Biochem 120: 467-473, 1996.
93. Panning B and Jaenisch R: RNA and the epigenetic regulation of X chromosome inactivation. Cell 93: 305-308, 1998.
94. Yoder JA, Walsh CP and Bestor TH: Cytosine methylation and the ecology of intragenomic parasites. Trends Genet 13: 335-340, 1997.
95. Lujambio A, Ropero S, Ballestar E, Fraga MF, Cerrato C, Setién F, Casado S, Suarez-Gauthier A, Sanchez-Cespedes M, Git A, *et al*: Genetic unmasking of an epigenetically silenced microRNA in human cancer cells. Cancer Res 67: 1424-1429, 2007.
96. Chen Z, Liu S, Tian L, Wu M, Ai F, Tang W, Zhao L, Ding J, Zhang L and Tang A: miR-124 and miR-506 inhibit colorectal cancer progression by targeting DNMT3B and DNMT1. Oncotarget 6: 38139-38150, 2015.
97. Zhu J, Zhang R, Yang D, Li J, Yan X, Jin K, Li W, Liu X, Zhao J, Shang W and Yu T: Knockdown of Long Non-coding RNA XIST inhibited doxorubicin resistance in colorectal cancer by upregulation of miR-124 and downregulation of SGK1. Cell Physiol Biochem 51: 113-128, 2018.
98. Zhang Y, Zheng L, Huang J, Gao F, Lin X, He L, Li D, Li Z, Ding Y and Chen L: MiR-124 Radiosensitizes human colorectal cancer cells by targeting PRRX1. PLoS One 9: e93917, 2014.
99. Xie XQ, Wang MJ, Li Y, Lei LP, Wang N, Lv ZY, Chen KL, Zhou B, Ping J, Zhou ZG and Sun XF: miR-124 intensified oxaliplatin-based chemotherapy by targeting CAPN2 in colorectal cancer. Mol Ther Oncolytics 17: 320-331, 2020.
100. Si M, Song Y, Wang X, Wang D, Liu X, Qu X, Song Z and Yu X: CXCL12/CXCR7/β-arrestin1 biased signal promotes epithelial-to-mesenchymal transition of colorectal cancer by repressing miRNAs through YAP1 nuclear translocation. Cell Biosci 12: 171, 2022.
101. Llovet JM, Montal R, Sia D and Finn RS: Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol 15: 599-616, 2018.
102. Vaquero J, Guedj N, Claperon A, Nguyen Ho-Bouldoires TH, Paradis V and Fouassier L: Epithelial-mesenchymal transition in cholangiocarcinoma: From clinical evidence to regulatory networks. J Hepatol 66: 424-441, 2017.
103. Wang H, Mao J, Huang Y, Zhang J, Zhong L, Wu Y, Huang H, Yang J, Wei Y and Tang J: Prognostic roles of miR-124-3p and its target ANXA7 and their effects on cell migration and invasion in hepatocellular carcinoma. Int J Clin Exp Pathol 13: 357-370, 2020.

104. Yue X, Cui Y, You Q, Lu Y and Zhang J: MicroRNA-124 negatively regulates chloride intracellular channel 1 to suppress the migration and invasion of liver cancer cells. Oncol Rep 42: 1380-1390, 2019.
105. Zheng F, Liao YJ, Cai MY, Liu YH, Liu TH, Chen SP, Bian XW, Guan XY, Lin MC, Zeng YX, *et al*: The putative tumour suppressor microRNA-124 modulates hepatocellular carcinoma cell aggressiveness by repressing ROCK2 and EZH2. Gut 61: 278-289, 2012.
106. Cao Q, Yu J, Dhanasekaran SM, Kim JH, Mani RS, Tomlins SA, Mehra R, Laxman B, Cao X, Yu J, *et al*: Repression of E-cadherin by the polycomb group protein EZH2 in cancer. Oncogene 27: 7274-7284, 2008.
107. Yu J, Cao Q, Mehra R, Laxman B, Yu J, Tomlins SA, Creighton CJ, Dhanasekaran SM, Shen R, Chen G, *et al*: Integrative genomics analysis reveals silencing of beta-adrenergic signaling by polycomb in prostate cancer. Cancer Cell 12: 419-431, 2007.
108. Thiery JP: Epithelial-mesenchymal transitions in tumour progression. Nat Rev Cancer 2: 442-454, 2002.
109. Chen G, Shi Y, Liu M and Sun J: circHIPK3 regulates cell proliferation and migration by sponging miR-124 and regulating AQP3 expression in hepatocellular carcinoma. Cell Death Dis 9: 175, 2018.
110. Agre P: The aquaporin water channels. Proc Am Thorac Soc 3: 5-13, 2006.
111. Magni F, Sarto C, Ticozzi D, Soldi M, Bosso N, Mocarelli P and Kienle MG: Proteomic knowledge of human aquaporins. Proteomics 6: 5637-5649, 2006.
112. Hu J and Verkman AS: Increased migration and metastatic potential of tumor cells expressing aquaporin water channels. FASEB J 20: 1892-1894, 2006.
113. Jablonski EM, Mattocks MA, Sokolov E, Koniaris LG, Hughes FM Jr, Fausto N, Pierce RH and McKillop IH: Decreased aquaporin expression leads to increased resistance to apoptosis in hepatocellular carcinoma. Cancer Lett 250: 36-46, 2007.
114. Chen XF, Li CF, Lu L and Mei ZC: Expression and clinical significance of aquaglyceroporins in human hepatocellular carcinoma. Mol Med Rep 13: 5283-5289, 2016.
115. Yu Q, Chen W, Li Y, He J, Wang Y, Yang S and Zhou J: The novel circular RNA HIPK3 accelerates the proliferation and invasion of hepatocellular carcinoma cells by sponging the micro RNA-124 or micro RNA-506/pyruvate dehydrogenase kinase 2 axis. Bioengineered 13: 4717-4729, 2022.
116. Liang T, Wang Y, Jiao Y, Cong S, Jiang X, Dong L, Zhang G and Xiao D: LncRNA MALAT1 accelerates cervical carcinoma proliferation by suppressing miR-124 expression in cervical tumor cells. J Oncol 2021: 8836078, 2021.
117. Wang Z, Li S and Zhang G: LncRNA DSCAM-AS1 negatively interacts with miR-124 to promote hepatocellular carcinoma proliferation. Crit Rev Eukaryot Gene Expr 32: 1-8, 2022.
118. Li J, Feng Q, Wei X and Yu Y: MicroRNA-490 regulates lung cancer metastasis by targeting poly r(C)-binding protein 1. Tumour Biol 37: 15221-15228, 2016.
119. Tabchi S, Kassouf E, Rassy EE, Kourie HR, Martin J, Campeau MP, Tehfe M and Blais N: Management of stage III non-small cell lung cancer. Semin Oncol 44: 163-177, 2017.
120. Gridelli C, Rossi A, Carbone DP, Guarize J, Karachaliou N, Mok T, Petrella F, Spaggiari L and Rosell R: Non-small-cell lung cancer. Nat Rev Dis Primers 1: 15009, 2015.
121. Ramnath N, Dilling TJ, Harris LJ, Kim AW, Michaud GC, Balekian AA, Diekemper R, Detterbeck FC and Arenberg DA: Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 143 (5 Suppl):e314S-e40S, 2013.
122. Kaplan JA, Liu R, Freedman JD, Padera R, Schwartz J, Colson YL and Grinstaff MW: Prevention of lung cancer recurrence using cisplatin-loaded superhydrophobic nanofiber meshes. Biomaterials 76: 273-281, 2016.
123. Deng XF, Jiang L, Liu QX, Zhou D, Hou B, Cui K, Min JX and Dai JG: Lymph node micrometastases are associated with disease recurrence and poor survival for early-stage non-small cell lung cancer patients: A meta-analysis. J Cardiothorac Surg 11: 28, 2016.
124. Yang Q, Wan L, Xiao C, Hu H, Wang L, Zhao J, Lei Z and Zhang HT: Inhibition of LHX2 by miR-124 suppresses cellular migration and invasion in non-small cell lung cancer. Oncol Lett 14: 3429-3436, 2017.
125. Kim BN, Ahn DH, Kang N, Yeo CD, Kim YK, Lee KY, Kim TJ, Lee SH, Park MS, Yim HW, *et al*: TGF-β induced EMT and stemness characteristics are associated with epigenetic regulation in lung cancer. Sci Rep 10: 10597, 2020.
126. Zu L, Xue Y, Wang J, Fu Y, Wang X, Xiao G, Hao M, Sun X, Wang Y, Fu G and Wang J: The feedback loop between miR-124 and TGF-β pathway plays a significant role in non-small cell lung cancer metastasis. Carcinogenesis 37: 333-343, 2016.
127. Wang P, Chen L, Zhang J, Chen H, Fan J, Wang K, Luo J, Chen Z, Meng Z and Liu L: Methylation-mediated silencing of the miR-124 genes facilitates pancreatic cancer progression and metastasis by targeting Rac1. Oncogene 33: 514-524, 2014.
128. Wilting SM, van Boerdonk RA, Henken FE, Meijer CJ, Diosdado B, Meijer GA, le Sage C, Agami R, Snijders PJ and Steenbergen RD: Methylation-mediated silencing and tumour suppressive function of hsa-miR-124 in cervical cancer. Mol Cancer 9: 167, 2010.
129. Qi MM, Ge F, Chen XJ, Tang C and Ma J: MiR-124 changes the sensitivity of lung cancer cells to cisplatin through targeting STAT3. Eur Rev Med Pharmacol Sci 23: 5242-5250, 2019.
130. Yu H, Chen Y and Jiang P: Circular RNA HIPK3 exerts oncogenic properties through suppression of miR-124 in lung cancer. Biochem Biophys Res Commun 506: 455-462, 2018.
131. Wu J, Weng Y, He F, Liang D and Cai L: LncRNA MALAT-1 competitively regulates miR-124 to promote EMT and development of non-small-cell lung cancer. Anticancer Drugs 29: 628-636, 2018.
132. Li H, Guo X, Li Q, Ran P, Xiang X, Yuan Y, Dong T, Zhu B, Wang L, Li F, *et al*: Long non-coding RNA 1308 promotes cell invasion by regulating the miR-124/ADAM 15 axis in non-small-cell lung cancer cells. Cancer Manag Res 10: 6599-6609, 2018.
133. Liu Y, Li L and Song XL: Exosomal circPVT1 derived from lung cancer promotes the progression of lung cancer by targeting miR-124-3p/EZH2 axis and regulating macrophage polarization. Cell Cycle 21: 514-530, 2022.
134. Kim K, Zang R, Choi SC, Ryu SY and Kim JW: Current status of gynecological cancer in China. J Gynecol Oncol 20: 72-76, 2009.
135. Heintz AP, Odicino F, Maisonneuve P, Quinn MA, Benedet JL, Creasman WT, Ngan HY, Pecorelli S and Beller U: Carcinoma of the ovary. FIGO 26th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet 95 (Suppl 1): S161-S192, 2006.
136. Stewart C, Ralyea C and Lockwood S: Ovarian cancer: An integrated review. Semin Oncol Nurs 35: 151-156, 2019.
137. Zaman MS, Maher DM, Khan S, Jaggi M and Chauhan SC: Current status and implications of microRNAs in ovarian cancer diagnosis and therapy. J Ovarian Res 5: 44, 2012.
138. Iorio MV, Visone R, Di Leva G, Donati V, Petrocca F, Casalini P, Taccioli C, Volinia S, Liu CG, Alder H, *et al*: MicroRNA signatures in human ovarian cancer. Cancer Res 67: 8699-8707, 2007.
139. Zhang L, Volinia S, Bonome T, Calin GA, Greshock J, Yang N, Liu CG, Giannakakis A, Alexiou P, Hasegawa K, *et al*: Genomic and epigenetic alterations deregulate microRNA expression in human epithelial ovarian cancer. Proc Natl Acad Sci USA 105: 7004-7009, 2008.
140. Mezzanzanica D, Bagnoli M, De Cecco L, Valeri B and Canevari S: Role of microRNAs in ovarian cancer pathogenesis and potential clinical implications. Int J Biochem Cell Biol 42: 1262-1272, 2010.
141. Kunej T, Godnic I, Ferdin J, Horvat S, Dovc P and Calin GA: Epigenetic regulation of microRNAs in cancer: An integrated review of literature. Mutat Res 717: 77-84, 2011.
142. Zhang H, Wang Q, Zhao Q and Di W: MiR-124 inhibits the migration and invasion of ovarian cancer cells by targeting SphK1. J Ovarian Res 6: 84, 2013.
143. Deng X, Chen Y, Liu Z and Xu J: MiR-124-3p.1 sensitizes ovarian cancer cells to mitochondrial apoptosis induced by carboplatin. Onco Targets Ther 13: 5375-5386, 2020.
144. Chen L and Kong C: LINC00173 regulates polycystic ovarian syndrome progression by promoting apoptosis and repressing proliferation in ovarian granulosa cells via the microRNA-124-3p (miR-124-3p)/jagged canonical Notch ligand 1 (JAG1) pathway. Bioengineered 13: 10373-10385, 2022.
145. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2020. CA Cancer J Clin 70: 7-30, 2020.
146. Gomella LG, Petrylak DP and Shayegan B: Current management of advanced and castration resistant prostate cancer. Can J Urol 21 (2 Suppl 1): S1-S6, 2014.

147. Scher HI, Buchanan G, Gerald W, Butler LM and Tilley WD: Targeting the androgen receptor: Improving outcomes for castration-resistant prostate cancer. Endocr Relat Cancer 11: 459-476, 2004.
148. Salinas CA, Tsodikov A, Ishak-Howard M and Cooney KA: Prostate cancer in young men: An important clinical entity. Nat Rev Urol 11: 317-323, 2014.
149. Han M, Partin AW, Pound CR, Epstein JI and Walsh PC: Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. Urol Clin North Am 28: 555-565, 2001.
150. Zhang W, Mao YQ, Wang H, Yin WJ, Zhu SX and Wang WC: MiR-124 suppresses cell motility and adhesion by targeting Talin 1 in prostate cancer cells. Cancer Cell Int 15: 49, 2015.
151. Shi XB, Ma AH, Xue L, Li M, Nguyen HG, Yang JC, Tepper CG, Gandour-Edwards R, Evans CP, Kung HJ and deVere White RW: miR-124 and androgen receptor signaling inhibitors repress prostate cancer growth by downregulating androgen receptor splice variants, EZH2, and Src. Cancer Res 75: 5309-5317, 2015.
152. Yan K, Hou L, Liu T, Jiao W, Ma Q, Fang Z, Zhang S, Song D, Liu J, Gao X and Fan Y: lncRNA OGFRP1 functions as a ceRNA to promote the progression of prostate cancer by regulating SARM1 level via miR-124-3p. Aging (Albany NY) 12: 8880-8892, 2020.
153. Shield KD, Ferlay J, Jemal A, Sankaranarayanan R, Chaturvedi AK, Bray F and Soerjomataram I: The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. CA Cancer J Clin 67: 51-64, 2017.
154. Solomon B, Young RJ and Rischin D: Head and neck squamous cell carcinoma: Genomics and emerging biomarkers for immunomodulatory cancer treatments. Semin Cancer Biol 52: 228-240, 2018.
155. Alsahafi E, Begg K, Amelio I, Raulf N, Lucarelli P, Sauter T and Tavassoli M: Clinical update on head and neck cancer: Molecular biology and ongoing challenges. Cell Death Dis 10: 540, 2019.
156. Salazar C, Nagadia R, Pandit P, Cooper-White J, Banerjee N, Dimitrova N, Coman WB and Punyadeera C: A novel saliva-based microRNA biomarker panel to detect head and neck cancers. Cell Oncol (Dordr) 37: 331-338, 2014.
157. Yoshizawa JM and Wong DT: Salivary microRNAs and oral cancer detection. Methods Mol Biol 936: 313-324, 2013.
158. Lopez-Cortes A, Guerrero S, Redal MA, Alvarado AT and Quinones LA: State of art of cancer pharmacogenomics in Latin American Populations. Int J Mol Sci 18: 639, 2017.
159. Salazar-Ruales C, Arguello JV, Lopez-Cortes A, Cabrera-Andrade A, Garcia-Cardenas JM, Guevara-Ramirez P, Peralta P, Leone PE and Paz-Y-Miño C: Salivary MicroRNAs for Early detection of head and neck squamous cell carcinoma: A case-control study in the high altitude mestizo Ecuadorian population. Biomed Res Int 2018: 9792730, 2018.
160. Zhao Y, Ling Z, Hao Y, Pang X, Han X, Califano JA, Shan L and Gu X: MiR-124 acts as a tumor suppressor by inhibiting the expression of sphingosine kinase 1 and its downstream signaling in head and neck squamous cell carcinoma. Oncotarget 8: 25005-25020, 2017.
161. Yang S, Yuan ZJ, Zhu YH, Chen X and Wang W: lncRNA PVT1 promotes cetuximab resistance of head and neck squamous cell carcinoma cells by inhibiting miR-124-3p. Head Neck 43: 2712-2723, 2021.
162. Chen W, Yang J, Fang H, Li L and Sun J: Relevance function of Linc-ROR in the pathogenesis of cancer. Front Cell Dev Biol 8: 696, 2020.
163. Zare A, Ahadi A, Larki P, Omrani MD, Zali MR, Alamdari NM and Ghaedi H: The clinical significance of miR-335, miR-124, miR-218 and miR-484 downregulation in gastric cancer. Mol Biol Rep 45: 1587-1595, 2018.
164. Wu Q, Zhong H, Jiao L, Wen Y, Zhou Y, Zhou J, Lu X, Song X and Ying B: MiR-124-3p inhibits the migration and invasion of Gastric cancer by targeting ITGB3. Pathol Res Pract 216: 152762, 2020.
165. Clevers H: Wnt/beta-catenin signaling in development and disease. Cell 127: 469-480, 2006.
166. Clevers H and Nusse R: Wnt/beta-catenin signaling and disease. Cell 149: 1192-1205, 2012.
167. Osaki M, Oshimura M and Ito H: PI3K-Akt pathway: Its functions and alterations in human cancer. Apoptosis 9: 667-676, 2004.
168. Dai J, Qian C, Su M, Chen M and Chen J: Gastrokine-2 suppresses epithelial mesenchymal transition through PI3K/AKT/GSK3β signaling in gastric cancer. Tumour Biol 37: 12403-12410, 2016.
169. Slomovitz BM and Coleman RL: The PI3K/AKT/mTOR pathway as a therapeutic target in endometrial cancer. Clin Cancer Res 18: 5856-5864, 2012.
170. Kang S, Dong SM, Kim BR, Park MS, Trink B, Byun HJ and Rho SB: Thioridazine induces apoptosis by targeting the PI3K/Akt/mTOR pathway in cervical and endometrial cancer cells. Apoptosis 17: 989-997, 2012.
171. Bader AG, Kang S, Zhao L and Vogt PK: Oncogenic PI3K deregulates transcription and translation. Nat Rev Cancer 5: 921-929, 2005.
172. Parsons R: Phosphatidylinositol 3-kinase inhibitors are a triple threat to ovarian cancer. Clin Cancer Res 11: 7965-7966, 2005.
173. Hoesel B and Schmid JA: The complexity of NF-kappaB signaling in inflammation and cancer. Mol Cancer 12: 86, 2013.
174. Romagnoli M, Belguise K, Yu Z, Wang X, Landesman-Bollag E, Seldin DC, Chalbos D, Barillé-Nion S, Jézéquel P, Seldin ML and Sonenshein GE: Epithelial-to-mesenchymal transition induced by TGF-β1 is mediated by Blimp-1-dependent repression of BMP-5. Cancer Res 72: 6268-6278, 2012.
175. Tobar N, Villar V and Santibanez JF: ROS-NFkappaB mediates TGF-beta1-induced expression of urokinase-type plasminogen activator, matrix metalloproteinase-9 and cell invasion. Mol Cell Biochem 340: 195-202, 2010.
176. Yu H and Jove R: The STATs of cancer-new molecular targets come of age. Nat Rev Cancer 4: 97-105, 2004.
177. Rudan I, Sidhu S, Papana A, Meng SJ, Xin-Wei Y, Wang W, Campbell-Page RM, Demaio AR, Nair H, Sridhar D, *et al*: Prevalence of rheumatoid arthritis in low- and middle-income countries: A systematic review and analysis. J Glob Health 5: 010409, 2015.
178. Yar Saglam AS, Alp E, Elmazoglu Z and Menevse S: Treatment with cucurbitacin B alone and in combination with gefitinib induces cell cycle inhibition and apoptosis via EGFR and JAK/STAT pathway in human colorectal cancer cell lines. Hum Exp Toxicol 35: 526-543, 2016.
179. Saravanan S, Islam VI, Babu NP, Pandikumar P, Thirugnanasambantham K, Chellappandian M, Raj CS, Paulraj MG and Ignacimuthu S: Swertiamarin attenuates inflammation mediators via modulating NF-κB/IκB and JAK2/STAT3 transcription factors in adjuvant induced arthritis. Eur J Pharm Sci 56: 70-86, 2014.
180. Wang Z, Li Y, Kong D, Ahmad A, Banerjee S and Sarkar FH: Cross-talk between miRNA and Notch signaling pathways in tumor development and progression. Cancer Lett 292: 141-148, 2010.
181. Kume T: Novel insights into the differential functions of Notch ligands in vascular formation. J Angiogenes Res 1: 8, 2009.
182. Lu ML, Zhang Y, Li J, Fu Y, Li WH, Zhao GF, Li XH, Wei L, Liu GB and Huang H: MicroRNA-124 inhibits colorectal cancer cell proliferation and suppresses tumor growth by interacting with PLCB1 and regulating Wnt/β-catenin signaling pathway. Eur Rev Med Pharmacol Sci 23: 121-136, 2019.
183. Lemieux E, Cagnol S, Beaudry K, Carrier J and Rivard N: Oncogenic KRAS signalling promotes the Wnt/β-catenin pathway through LRP6 in colorectal cancer. Oncogene 34: 4914-4927, 2015.
184. Shahmohamadnejad S, Nouri Ghonbalani Z, Tahbazlahafi B, Panahi G, Meshkani R, Emami Razavi A, Shokri Afra H and Khalili E: Aberrant methylation of miR-124 upregulates DNMT3B in colorectal cancer to accelerate invasion and migration. Arch Physiol Biochem 128: 1503-1509, 2022.
185. Hernandez-Caballero ME, Sierra-Ramirez JA, Villalobos-Valencia R and Sesena-Mendez E: Potential of *Kalanchoe pinnata* as a cancer treatment adjuvant and an epigenetic regulator. Molecules 27: 6425, 2022.
186. Zeng L, Fagotto F, Zhang T, Hsu W, Vasicek TJ, Perry WL III, Lee JJ, Tilghman SM, Gumbiner BM and Costantini F: The mouse Fused locus encodes Axin, an inhibitor of the Wnt signaling pathway that regulates embryonic axis formation. Cell 90: 181-192, 1997.
187. Duchartre Y, Kim YM and Kahn M: The Wnt signaling pathway in cancer. Crit Rev Oncol Hematol 99: 141-149, 2016.
188. Lang Q and Ling C: MiR-124 suppresses cell proliferation in hepatocellular carcinoma by targeting PIK3CA. Biochem Biophys Res Commun 426: 247-252, 2012.
189. Napetschnig J and Wu H: Molecular basis of NF-kappaB signaling. Annu Rev Biophys 42: 443-468, 2013.

190. Hinz M, Stilmann M, Arslan SC, Khanna KK, Dittmar G and Scheidereit C: A cytoplasmic ATM-TRAF6-cIAP1 module links nuclear DNA damage signaling to ubiquitin-mediated NF-kappaB activation. Mol Cell 40: 63-74, 2010.
191. Xie C, Zhang LZ, Chen ZL, Zhong WJ, Fang JH, Zhu Y, Xiao MH, Guo ZW, Zhao N, He X and Zhuang SM: A hMTR4-PDIA3P1-miR-125/124-TRAF6 regulatory axis and its function in NF kappa B signaling and chemoresistance. Hepatology 71: 1660-1677, 2020.
192. Lv Y, Chen S, Wu J, Lin R, Zhou L, Chen G, Chen H and Ke Y: Upregulation of long non-coding RNA OGFRP1 facilitates endometrial cancer by regulating miR-124-3p/SIRT1 axis and by activating PI3K/AKT/GSK-3β pathway. Artif Cells Nanomed Biotechnol 47: 2083-2090, 2019.
193. Li Y, Zhang Z, Liu X, Huang T, He W, Shen Y, Liu X, Hong K and Cao Q: miR-124 functions as a tumor suppressor in the endometrial carcinoma cell line HEC-1B partly by suppressing STAT3. Mol Cell Biochem 388: 219-231, 2014.
194. Yuan D, Zhu D, Yin B, Ge H, Zhao Y, Huang A, Wang X, Cao X, Xia N and Qian H: Expression of lncRNA NEAT1 in endometriosis and its biological functions in ectopic endometrial cells as mediated via miR-124-3p. Genes Genomics 44: 527-537, 2022.
195. Hu YZ, Hu ZL, Liao TY, Li Y and Pan YL: LncRNA SND1-IT1 facilitates TGF-beta1-induced epithelial-to-mesenchymal transition via miR-124/COL4A1 axis in gastric cancer. Cell Death Discov 8: 73, 2022.
196. Jiang L, Lin T, Xu C, Hu S, Pan Y and Jin R: miR-124 interacts with the Notch1 signalling pathway and has therapeutic potential against gastric cancer. J Cell Mol Med 20: 313-322, 2016.
197. Xiao HJ, Ji Q, Yang L, Li RT, Zhang C and Hou JM: In vivo and in vitro effects of microRNA-124 on human gastric cancer by targeting JAG1 through the Notch signaling pathway. J Cell Biochem 119: 2520-2534, 2018.
198. Zheng YB, Xiao GC, Tong SL, Ding Y, Wang QS, Li SB and Hao ZN: Paeoniflorin inhibits human gastric carcinoma cell proliferation through up-regulation of microRNA-124 and suppression of PI3K/Akt and STAT3 signaling. World J Gastroenterol 21: 7197-7207, 2015.
199. Wu Z, Huang W, Chen B, Bai PD, Wang XG and Xing JC: Up-regulation of miR-124 inhibits invasion and proliferation of prostate cancer cells through mediating JAK-STAT3 signaling pathway. Eur Rev Med Pharmacol Sci 21: 2338-2345, 2017.
200. Qin Z and Liu X: miR-124, a potential therapeutic target in colorectal cancer. Onco Targets Ther 12: 749-751, 2019.
201. Zhou Z, Lv J, Wang J, Yu H, Lu H, Yuan B, Han J, Zhou R, Zhang X, Yang X, *et al*: Role of MicroRNA-124 as a prognostic factor in multiple neoplasms: A meta-analysis. Dis Markers 2019: 1654780, 2019.
202. Jiao D, Li Z, Zhu M, Wang Y, Wu G and Han X: LncRNA MALAT1 promotes tumor growth and metastasis by targeting miR-124/foxq1 in bladder transitional cell carcinoma (BTCC). Am J Cancer Res 8: 748-760, 2018.
203. Gao XR, Wang HP, Zhang SL, Wang MX and Zhu ZS: Pri-miR-124 rs531564 polymorphism and colorectal cancer risk. Sci Rep 5: 14818, 2015.
204. Long HD, Ma YS, Yang HQ, Xue SB, Liu JB, Yu F, Lv ZW, Li JY, Xie RT, Chang ZY, *et al*: Reduced hsa-miR-124-3p levels are associated with the poor survival of patients with hepatocellular carcinoma. Mol Biol Rep 45: 2615-2623, 2018.
205. Cong C, Wang W, Tian J, Gao T, Zheng W and Zhou C: Identification of serum miR-124 as a biomarker for diagnosis and prognosis in osteosarcoma. Cancer Biomark 21: 449-454, 2018.
206. Davis FG and McCarthy BJ: Current epidemiological trends and surveillance issues in brain tumors. Expert Rev Anticancer Ther 1: 395-401, 2001.
207. Chen T, Wang XY, Li C and Xu SJ: Downregulation of microRNA-124 predicts poor prognosis in glioma patients. Neurol Sci 36: 131-135, 2015.
208. Romero-Lopez MJ, Jimenez-Wences H, Cruz-De la Rosa MI, Roman-Fernandez IV and Fernandez-Tilapa G: miR-23b-3p, miR-124-3p and miR-218-5p synergistic or additive effects on cellular processes that modulate cervical cancer progression? A molecular balance that needs attention. Int J Mol Sci 23: 13551, 2022.
209. Ruan F, Wang YF and Chai Y: Diagnostic values of miR-21, miR-124, and M-CSF in patients with early cervical cancer. Technol Cancer Res Treat 19: 1533033820914983, 2020.
210. Liang F, Zhang H, Qiu Y, Xu Q, Jian K, Jiang L, Wang F and Lu X: MiR-124-5p inhibits the progression of gastric cancer by targeting MIEN1. Technol Cancer Res Treat 19: 1533033820979199, 2020.
211. Liu F, Hu H, Zhao J, Zhang Z, Ai X, Tang L and Xie L: miR-124-3p acts as a potential marker and suppresses tumor growth in gastric cancer. Biomed Rep 9: 147-155, 2018.
212. Wu DH, Liang H, Lu SN, Wang H, Su ZL, Zhang L, Ma JQ, Guo M, Tai S and Yu S: miR-124 suppresses pancreatic ductal adenocarcinoma growth by regulating monocarboxylate transporter 1-mediated cancer lactate metabolism. Cell Physiol Biochem 50: 924-935, 2018.
213. Zhang YH, Wang QQ, Li H, Ye T, Gao F and Liu YC: miR-124 radiosensitizes human esophageal cancer cell TE-1 by targeting CDK4. Genet Mol Res: 15, 2016 doi: 10.4238/gmr.15027893.
214. Gao C, Xu YJ, Qi L, Bao YF, Zhang L and Zheng L: CircRNA VIM silence synergizes with sevoflurane to inhibit immune escape and multiple oncogenic activities of esophageal cancer by simultaneously regulating miR-124/PD-L1 axis. Cell Biol Toxicol 38: 825-845, 2022.
215. Hu D, Li M, Su J, Miao K and Qiu X: Dual-targeting of miR-124-3p and ABCC4 promotes sensitivity to Adriamycin in breast cancer cells. Genet Test Mol Biomarkers 23: 156-165, 2019.
216. Du J, He Y, Wu W, Li P, Chen Y, Hu Z and Han Y: Targeting EphA2 with miR-124 mediates Erlotinib resistance in K-RAS mutated pancreatic cancer. J Pharm Pharmacol 71: 196-205, 2019.
217. Wang L, Wu M and Zhou X: Long non-coding RNA UCA1 promotes retinoblastoma progression by modulating the miR-124/c-myc axis. Am J Transl Res 14: 1592-1605, 2022.
218. Qian C, Wang Y, Ji Y, Chen D, Wang C, Zhang G and Wang Y: Neural stem cell-derived exosomes transfer miR-124-3p into cells to inhibit glioma growth by targeting FLOT2. Int J Oncol 61: 115, 2022.
219. Gupta D, Zickler AM and El Andaloussi S: Dosing extracellular vesicles. Adv Drug Deliv Rev 178: 113961, 2021.
220. Lasser C, Eldh M and Lotvall J: Isolation and characterization of RNA-containing exosomes. J Vis Exp 9: e3037, 2012.
221. Barile L and Vassalli G: Exosomes: Therapy delivery tools and biomarkers of diseases. Pharmacol Ther 174: 63-78, 2017.
222. Isaac R, Reis FCG, Ying W and Olefsky JM: Exosomes as mediators of intercellular crosstalk in metabolism. Cell Metab 33: 1744-1762, 2021.
223. Groot M and Lee H: Sorting mechanisms for MicroRNAs into extracellular vesicles and their associated diseases. Cells 9: 1044, 2020.
224. Shuang O, Zhou J, Cai Z, Liao L, Wang Y, Wang W and Xu M: EBF1-mediated up-regulation of lncRNA FGD5-AS1 facilitates osteosarcoma progression by regulating miR-124-3p/G3BP2 axis as a ceRNA. J Orthop Surg Res 17: 332, 2022.
225. Bronisz A, Godlewski J and Chiocca EA: Extracellular vesicles and MicroRNAs: Their role in tumorigenicity and therapy for brain tumors. Cell Mol Neurobiol 36: 361-376, 2016.
226. Ma Y, Shen N, Wicha MS and Luo M: The roles of the Let-7 family of MicroRNAs in the regulation of cancer stemness. Cells 10: 2415, 2021.
227. Masliah-Planchon J, Garinet S and Pasmant E: RAS-MAPK pathway epigenetic activation in cancer: miRNAs in action. Oncotarget 7: 38892-38907, 2016.
228. Kanlikilicer P, Rashed MH, Bayraktar R, Mitra R, Ivan C, Aslan B, Zhang X, Filant J, Silva AM, Rodriguez-Aguayo C, *et al*: Ubiquitous release of Exosomal tumor suppressor miR-6126 from ovarian cancer cells. Cancer Res 76: 7194-7207, 2016.
229. Yin Y, Liu B, Cao Y, Yao S, Liu Y, Jin G, Qin Y, Chen Y, Cui K, Zhou L, *et al*: Colorectal Cancer-derived small extracellular vesicles promote tumor immune evasion by upregulating PD-L1 expression in tumor-associated macrophages. Adv Sci (Weinh) 9: 2102620, 2022.
230. Urabe F, Kosaka N, Sawa Y, Yamamoto Y, Ito K, Yamamoto T, Kimura T, Egawa S and Ochiya T: miR-26a regulates extracellular vesicle secretion from prostate cancer cells via targeting SHC4, PFDN4, and CHORDC1. Sci Adv 6: eaay3051, 2020.
231. Jiang F and Doudna JA: CRISPR-Cas9 Structures and Mechanisms. Annu Rev Biophys 46: 505-529, 2017.
232. Wang SW, Gao C, Zheng YM, Yi L, Lu JC, Huang XY, Cai JB, Zhang PF, Cui YH and Ke AW: Current applications and future perspective of CRISPR/Cas9 gene editing in cancer. Mol Cancer 21: 57, 2022.

233. Horodecka K and Duchler M: CRISPR/Cas9: Principle, applications, and delivery through extracellular vesicles. Int J Mol Sci 22: 6072, 2021.
234. Bao A, Burritt DJ, Chen H, Zhou X, Cao D and Tran LP: The CRISPR/Cas9 system and its applications in crop genome editing. Crit Rev Biotechnol 39: 321-336, 2019.
235. Chen M, Mao A, Xu M, Weng Q, Mao J and Ji J: CRISPR-Cas9 for cancer therapy: Opportunities and challenges. Cancer Lett 447: 48-55, 2019.
236. Li W, Cho MY, Lee S, Jang M, Park J and Park R: CRISPR-Cas9 mediated CD133 knockout inhibits colon cancer invasion through reduced epithelial-mesenchymal transition. PLoS One 14: e0220860, 2019.
237. Zhou SJ, Deng YL, Liang HF, Jaoude JC and Liu FY: Hepatitis B virus X protein promotes CREB-mediated activation of miR-3188 and Notch signaling in hepatocellular carcinoma. Cell Death Differ 24: 1577-1587, 2017.
238. Liu C, Ding X, Wei C, Pei Y, Meng F, Zhong Y and Liu Y: LncRNA LNCOC1 is Upregulated in melanoma and serves as a potential regulatory target of miR-124 to suppress cancer cell invasion and migration. Clin Cosmet Investig Dermatol 15: 751-762, 2022.
239. Gupta D, Bhattacharjee O, Mandal D, Sen MK, Dey D, Dasgupta A, Kazi TA, Gupta R, Sinharoy S, Acharya K, *et al*: CRISPR-Cas9 system: A new-fangled dawn in gene editing. Life Sci 232: 116636, 2019.
240. Huo W, Zhao G, Yin J, Ouyang X, Wang Y, Yang C, Wang B, Dong P, Wang Z, Watari H, *et al*: Lentiviral CRISPR/Cas9 vector mediated miR-21 gene editing inhibits the epithelial to mesenchymal transition in ovarian cancer cells. J Cancer 8: 57-64, 2017.
241. Kunej T, Godnic I, Horvat S, Zorc M and Calin GA: Cross talk between microRNA and coding cancer genes. Cancer J 18: 223-231, 2012.
242. Hu S, Zang R, Wang Y, Liang Y, Mu J, Zhang Y and Ma J: Highly expressed microRNA-124 inhibits migration and promotes apoptosis of esophageal cancer cells by degrading PDCD6. J BUON 24: 805-812, 2019.
243. Zhao X, He W, Li J, Huang S, Wan X, Luo H and Wu D: MiRNA-125b inhibits proliferation and migration by targeting SphK1 in bladder cancer. Am J Transl Res 7: 2346-2354, 2015.
244. Liu Z, Guo S, Sun H, Bai Y, Song Z and Liu X: Circular RNA CircHIPK3 elevates CCND2 expression and promotes cell proliferation and invasion through miR-124 in Glioma. Front Genet 11: 1013, 2020.
245. Sanuki R and Yamamura T: Tumor suppressive effects of miR-124 and its function in neuronal development. Int J Mol Sci 22: 5919, 2021.
246. Yong T, Sun A, Henry MD, Meyers S and Davis JN: Down regulation of CSL activity inhibits cell proliferation in prostate and breast cancer cells. J Cell Biochem 112: 2340-2351, 2011.
247. Gao Y, Yang M, Wei L, Liang X, Wu F, Huang Y and Yang T: miR-34a-5p inhibits cell proliferation, migration and invasion through targeting JAG1/Notch1 pathway in HPV-infected human epidermal keratinocytes. Pathol Oncol Res 26: 1851-1859, 2020.
248. Cheng Z, Li X, Ye X, Yu R and Deng Y: Purpurogallin reverses neuronal apoptosis and enhances 'M2' polarization of microglia under ischemia via mediating the miR-124-3p/TRAF6/NF-kappaB axis. Neurochem Res 48: 375-392, 2023.
249. Wu Z, Huang W, Chen B, Bai PD, Wang XG and Xing JC: Up-regulation of miR-124 inhibits invasion and proliferation of prostate cancer cells through mediating JAK-STAT3 signaling pathway. Eur Rev Med Pharmacol Sci 24: 7546, 2020.
250. Gao S, Yu J, Shan Z, Zuo L, Huang W, Gan L and Tian H: IncRNA XIST targets miR-124/JAG1 via CeRNA mechanism to facilitate the migration and proliferation of tongue squamous cell carcinoma. Clin Lab: 68, 2022 doi: 10.7754/Clin.Lab.2021.210325.
251. Guo W, Liu GM, Guan JY, Chen YJ, Zhao YZ, Wang K and Bai O: Epigenetic regulation of cutaneous T-cell lymphoma is mediated by dysregulated lncRNA MALAT1 through modulation of tumor microenvironment. Front Oncol 12: 977266, 2022.
252. Zhang WL, Zhao YN, Shi ZZ, Gu GY, Cong D, Wei C and Bai YS: HOXA11-AS promotes the migration and invasion of hepatocellular carcinoma cells by inhibiting miR-124 expression by binding to EZH2. Hum Cell 32: 504-514, 2019.
253. Ghafouri-Fard S, Shoorei H, Bahroudi Z, Abak A, Majidpoor J and Taheri M: An update on the role of miR-124 in the pathogenesis of human disorders. Biomed Pharmacother 135: 111198, 2021.