MIR-124 DEFICIENCY POTENTIALLY PROMOTES THE PROGRESSIONS OF CERTAIN CANCERS

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ABSTRACT

MicroRNAs (miRNAs) play important roles in carcinogenesis. Up to date, miR-124 deregulation has been linked to the malignancy of breast cancer (BC), nasopharyngeal cancer (NPC), bladder cancer (BCa), colorectal cancer (CRC), non-small cell lung cancer (NSCLC), gliobastoma (GB) and hepatocellular carcinoma (HCC). Potentially acting as a tumor growth suppressor, miR-124 was commonly down-regulated in clinical surgical specimens from patients suffering with above cancers. MiR-124 deficiency enhanced the development and progressions of BC, NPC, BCa, NSCLC, CRC, GB and HCC and contributes in the advance of patient's TNM stage. MiR-124 expression level was reversely correlated with lymph node metastasis of NSCLC patients and survival time of BC patients. MiR-124 was generally down-regulated in above cancer cell lines. Consequently, restored miR-124 over-expression led to the increased *in vitro* apoptosis, decreased *in vitro* proliferation, migration and invasion capacities and the decreased *in vivo* tumorigenesis and malignancy of corresponding cancer cell lines. MiR-124 functions in carcinogenesis through the interactions with diverse genes and proteins. STAT3 was most commonly regulated by miR-124 dysexpression in above cancers, followed by sp1, CD151, CDK4 and NF-kB. LncRNAs including MALAT1, NEATI and HOXA11-ASwere involved in miR-124-mediated tumorigenesis for NPC and NSCLC. MiR-124 plays an important role in tumor cell malignancy and cancer development and progression. Its use in the understanding of carcinogenesis, diagnosis and treatment of cancers is worthy of further study.

Key words: Carcinogenesis, miR-124, breast cancer, nasopharyngeal cancer, bladder cancer, colorectal cancer

INTRODUCTION

The term of "miRNA", abbreviation of microRNA, appeared in 2001[1-3]. While, miRNAs were discovered as a comprehensive novel type of regulatory control for gene expression [4]. During plant and animal development and investigated since 1993. Lin-4was the first miRNA reported [5, 6]. As a class of small non-coding RNAs post-transcriptionally targeting the protein-coding gene *via* negatively regulating its expression [7, 8]miRNAs are small non-coding RNAs composed of 19-24 nucleotides. They directly target motifs in mRNAs and suppress gene expression post-transcriptionally by transcript degradation or translation repression [9, 10]. The miRNA seed sequence, the 2nd to 8th nucleotide region at the 5′-end site of miRNA, determines its typicality for targeting mRNAs. The binding of miRNA to its targeting mRNAs resulted in the inhibition of translation, degradation/destabilization, or direct cleavage of the later [11-15]. MiRNAs are involved in multiple pathological and physiological processes [11, 16], through suppressing target genes *via* affecting cell differentiation, proliferation, mobility and apoptosis [17].

The discovery ofmiR-16 and miR-15suppressions in chronic lymphocytic leukemia were for the first time demonstrated the involvement of miRNAs in cancers [18]. Then, the role of miRNA in cancer has attracted a

vast consideration from researchers. MiRNAs might functionalize as a tumor promoter or suppressor in tumor malignancy depending on cancer type[19].For example, the dysregulation of miR-9, miR-10b, miR-26a, miR-214, miR-144, miR-200 family and miR-124contributed to the development of a variety of cancers including liver cancer, nasopharyngeal carcinoma and renal cell carcinoma [20-28].The study on the role and molecular underlying mechanism of miRNAs in carcinogenesis deserves more attention, and contributes to the better understanding, diagnosis and treatment of cancer.

MiR-124 has three members' miR-124-1, miR-124-2 and miR-124-3 [29-31].Compared with other tissues, miR-124 is particularly highly expressed in pituitary gland and all brain regions [32, 33], which helps to explain its critical function in neurodevelopment and stem cell regulation [34, 35].MiR-124 dysregulation was involved in different human malignancies including tumorigenesis and progression [29-31, 36-41]. To date, miR-124 was commonly reported as tumor suppressor in cancer. It was found epigenetically suppressed and regulated the biological functions of cancer cells *via* targeting the genes such are ROCK2, EZH2, SPHK1, RAC1, AR and CD151 [36-40]. Current review summarized and interpreted the research, clinical association and underlying function mechanism of miR-124 in cancers.

MiR-124 deficiency promotes TNM stage and shortens survival time of breast cancer patients

Breast cancer (BC) is the leading cancer for women. Following the improvement and development in the diagnosis and joint treatment (chemotherapy, radiation and surgery), BC prognosis is encouraging. While, the morbidity and mortality of BC patients diagnosed with metastasis is still high by accounting for about 90% of total BC deaths [42].

MiR-124 malfunction was associated with BC clinical malignancy [43-45]. Collectively, miR-124 deficiency is associated with BC cancer cell malignancy and BC aggressiveness [36, 42-53]. As the study summarized in Table-1, miR-124 was decreased in clinical tumorous specimens from BC patients [46-48]. Moreover, its deficiency was reversely correlated with BC progression [48].Compared with tumorous specimens of BC patients with T1 stage, miR-124 level was significantly decreased in patients with II-IV stages [46-48]. Further analysis indicated miR-124 down-expression potentially contributed in enhanced lymph node metastasis and shortened overall survival for BC patients [47].

MiR-124 was also determined down-regulated in a variety of BC cancer cell lines [46, 47]. Consequently, showedmiR-124 restored over-expression potentially antagonized the malignant properties of cancer cell [46, 47, 49-52]. The over-expression of decreased the *in vitro*1) cell growth of MCF-7, MDA-MB-231, T47D and MDA-MB-435S cells [36, 46, 47, 49, 51-53], 2) cell migration of MCF-7, MDA-MB-231 and T47D cells[46, 47, 49, 51-53], cell invasion of MCF-7, [46, 47, 49, 51, 52], cell motility of MDA-MB-231, T47D and MCF-7 cells [36, 46, 52], cell viability, cell cycle progression of MCF-7 and MDA-MB-435S cells [53], and DNA repair capacity of MDA-MB-231 cells [49]. Consistently, miR-124 over-expression inhibited the *in vivo* tumorigenesis and metastasis capacities ofMCF-7 cells [51, 53].

MiR-124 was reported to be involved in tumor malignancy and progression through some well-known genes, proteins and pathways [36, 46, 48, 49, 51-53]. As summarized in Table-1, miR-124 over-expression decreased the *in vitro* malignant properties of1) MDA-MB-231 cells through down-regulating FLOT1 [46], CD151 [36], PARP1 and ATM interactor (ATMIN) [49], and AKT2 [51], 2) T47D cells by down-regulating FLOT1 [46], 3) MCF-7 cells by reducing the expression levels and activities of CBL [50], CD151[36], SNAI2 [52], AKT2[51] and CDK4 [53],4) MDA-MB-435S cells *via* suppressing CDK4 [53],and 5) SKBR3 cells *via* down-regulating STAT3 protein expression [48].

MiR-124 reduction is reversely correlated with nasopharyngeal carcinoma development

Nasopharyngeal carcinoma (NPC) is characterized with early distant metastasis and highly malignant local invasion by gravely endangering public health [52]. It is more highly prevalent in Southeast Asia, especially in southern China [54, 55]. Certain genetic and epigenetic abnormalities were reported to synergistically interrupt the function of normal cells, and to contribute in NPC [56-59] pathogenesis, tumorigenesis and progression. Up to now, the malfunction of miRNAs including miR-9, miR-26a, miR-10b, miR-144, miR-214 and miR-124are reported to be involved in the development and progression of NPC [22-24, 26, 27, 60-63].

As summarized in Table-1, miR-124 deficiency was commonly reported to be reversely correlated with the clinical aggressiveness of NPC patients and malignant properties of NPC cells. Compared with the tumorous specimens from NPC patients diagnosed with stage T1-T2, miR-124 expression level was significantly decreased in patients with stage T3-T4 [64]. MiR-124 was also determined down-regulated in NPC cancer cell lines [62, 63, 65]. Consequently, restored over-expression of miR-124 reduced the *in vitro* proliferation, migration and invasion capacities and *in vivo* tumorigenesis and metastasis of NPC cells [62-65]. MiR-124 over-expression inhibited the *in vitro* 1) migration, invasion, apoptosis and proliferation of C666-1 cells [63], 2) invasion and proliferation of HONE1 and CNE2 cells [62], 3) colony forming capacities of 5-8F and 6-10B cells [64]. The stable expression of miR-124 reduced the *in vivo* tumorigenesis, tumor growth velocity and size, and metastasis of NPC 5-8 F cells and SUNE2 cells [64, 65].

MiR-124 functions in NPC through the interaction with or mediation by other genes, protein or lncRNA [62-66]. Table-1 summarized the molecular signaling pathways for miR-124 in NPC malignancy. MiR-124 over-expression decreased the *in vitro* malignant properties of 1) C666-1 cells *via* down-regulating the protein expression levels of STAT3, p-STAT3, MMP-2 and CCND2 [53], 2) CNE2 and HONE1 cells *via* decreasing CAPN4 expression [62], 3) 5-8F and 6-10B cells *via* down-regulating FOXQ1 expression [64], 4) SUNE2 cells *via* suppressing NF-KB activation [65] and down-regulating FOXQ1 [64]. MiR-124 also acts through lncRNAs. The up-regulation of two lncRNAs, NEAT1 and MALTAT1, promoted the *in vivo* growth and tumorigenesis of SUNE2 cells. The over-expression of miR-124 reversed their influences [65, 66].

MiR-124 probably directly mediates CAPN4 in NPC as it can suppress the latter's expression and its inhibition on CNE2 and HONE1 proliferation and invasion can be reversed by the latter's over-expression [62]. By blocking E-cadherin transcription, FOXQ1 up-regulation enhanced NPC aggressiveness by enhancing epithelial-mesenchymal transition [21, 22]. By directly binding to the 3′-UTR domain of FOXQ1, MiR-124 up-regulation decreased FOXQ1 level and resulted in reduced *in vitro* and *in vivo* malignancy, tumorigenesis and invasion capacities of NPC cells [64]. Moreover, it was reported miR-124 function was associated with lncRNAs [65]. MALAT1 and NEATI have the direct interaction binding sites with miR-124 [65, 66]. The level decrease of miR-124 due to the sponging by up-regulated MALAT1 and NEAT1 resulted in enhanced proliferation [65, 66] and invasion [66], and decreased apoptosis of NPC cells [65].Collectively, miR-124 deficiency is associated with NPC cancer cell malignancy and NPC aggressiveness. It is of potential use as an indicator for NPC.

MiR-124 down-expression is associated with malignant progression of bladder cancer

As a common malignant tumor in urinary system, bladder cancer (BCa) is the second frequent death cause among tumors of genitourinary [67]. It presents a higher incidence rate of three to ten times in men than women [68].

Aberrant expression of miR-124 was involved in BCa aggressiveness and progression [69]. MiR-124 was down-regulated in both clinical tissues from BCa patients and BCa cancer cell lines [69, 70] by suggesting its deficiency in promoting BCa progression. MiR-124 deficiency was linked to increased proliferation and aggressiveness of J82, UM-UC-3, HT1197 and T24 cell lines [69-72]. The restored over-expression of miR-124in BCa cell lines decreased the *in vitro* proliferation, migration and invasion capacities of J82, UM-UC-3 and T24 cells [70] and motility of T24 cells [69] by arresting cell cycle at G1 phase [70, 72]. Concordantly, miR-124 over-expression promoted T24 cell apoptosis [69]. Moreover, miR-124 over-expression led to decreased *in vivo* tumorigenesis, tumor growth and size in tumor-bearing mice induced by HT1197 implantation [72].

MiR-124 functionalized in BCa through the following pathways [69-72]. For J82 and UM-UC-3 cells, miR-124 up-regulation abated their malignant properties through down-regulating ROCK1 [70]. MiR-124 over-expression decreased the proliferation, migration, invasion and motility capacities of T24 cells *via* depressing ROCK1 [70] and AURKA [69]. Through down-regulating CDK4 expression, miR-124 over-expression arrested HT1197 cells in G1 phase by interrupting its growth [72]. The function of miR-124 in BCa was reported mediated by lncRNA [71]. Androgen receptor (AR) up-regulation was decisively involved in BCa malignancy [73]. X-inactive specific transcript (XIST) lncRNA, a direct binding target of miR-124, was found to be able to decrease miR-124 expression and increase AR expression in TCC-SUP and UM-UC-3 cells [71]. The knockdown of XIST by miR-124 expression resulted in AR reduction and inhibited migration, invasion and proliferation capacities of TCC-SUP and UM-UC-3 cells. Meanwhile, XIST over-expression up-regulated AR level and abolished miR-124 biological inhibitory function on TCC-SUP and UM-UC-3 malignant behaviors [71]. MiR-124 is a potential independent marker in BCa.

MiR-124 deficiency contributes in promoting the TNM stage and lymph node metastasis of non-small cell lung cancer patients

Lung cancer ranks as the first leading cancer in the world. Non-small cell lung cancer (NSCLC) [74] accounts about 85% of all lung cancer cases. Characterized with retarded cell growth and division together with relative late spreading and metastasis, the majority of NSCLC patients were diagnosed in advanced stages with a poor 5-year survival rate of ~17% [75, 76].

MiR-124 potentially plays as a tumor suppressor role in NSCLC. Its deficiency contributes in the development and aggressiveness of NSCLC. Compared with paracancerous tissues and normal lung cell lines, the expression level of miR-124 were measured much lower in tumorous specimens of NSCLC patients and NSCLC cell lines, as the results summarized in Table-1. MiR-124 deficiency was reversely correlated with the clinical progression of NSCLC patients and malignant properties of NSCLC cells [41, 77, 78]. In clinical, compared with NSCLC patients diagnosed with stage T1-T2, miR-124 level was significantly decreased in tumorous tissues from patients with stage T3-T4. MiR-124 deficiency was negatively correlated with lymph node metastasis of NSCLC patients [41, 78]. Accordingly, miR-124 over-expression was validated to be able to suppress the *in vitro* proliferation, colony forming, migration and invasion abilities of A549, H322 and H1299 cells [41, 77-79]. Its over-expression resulted in enhanced apoptosis of H322 [79] and A549 cells [79, 80].

The molecular action mechanism of miR-124 in NSCLC was well investigated, as shown in Table-1. Either at protein level or at protein and mRNA expression levels, restored over-expression of miR-124 decreased the malignant properties of A549 cells through down-regulating Slug [77], CDH2 [41], LHX2 [81], STAT3 [79, 80], Sp1 [82], AKT1 and AKT2 [83], led to attenuated malignancy of H1299 cells *via* down-regulating CDH2

[78], LHX2 [81], CD164 [79] and MYO10 [84]. MiR-124 over-expression also led to decreased expressions of TXNRD1 in HCC827 and CALU3 cells [84], and of MYO10 in H522M3 and H1975M3 cells [84], respectively.

MiR-124 was also found to mediate NSCLC progression through the interaction with lncRNAs, MALAT1 and HOXA11-AS. MALAT1 and HOXA11-AS up-regulations in NSCLC patients' specimens were negatively correlated with miR-124 down-regulation [82, 85]. MALAT1 up-regulation was positively correlated with the up-regulation of STAT3, a direct target of miR-124, in A549, H23, H522, H1299 and H460 cells compared with normal lung 16HBE cells [85]. MALAT1 acts as a competing endogenous RNA to modulate miR-124/STAT3 in NSCLC. In A549 and H1299 cells, MALAT1 silence resulted in level increase of miR-124, and miR124 over-expression and down-expression led to the level decrease and increase for MALAT1, respectively [85]. The down-regulation of MALAT1 by miR-124 over-expression was reversed in A549 and H1299 cells transfected with miR-124 inhibitor [85]. MALAT1 knockdown probably attenuated the proliferation and colony forming capacities of A549 and H1299 cells by enhancing cell apoptosis *via* increasing miR-124 and decreasing STAT3 expressions [85], which can also be reversed by miR-124 knockdown in them [85]. Similarly, as another competing endogenous RNA, HOXA11-AS mediated miR-124 function in NSCLC malignancy through transcriptional factor SP. The concordant up-regulations of HOXA11-AS and SP1 were negatively correlated with miR-124 down-regulation in both NSCLC clinical specimens from patients and cancer cell lines [82]. HOXA11-AS knockdown by siRNA transient interference increased miR-124 expression level in H1299 [82]. Moreover, HOXA11-AS over-expression resulted in up-regulated SP1 and enhanced the proliferation, colony forming and invasion capacities of A549 cells, which could be suppressed by miR-124 over-expression in A549 cells [82].

MiR-124 deficiency is negatively correlated with the progression of colorectal cancer patients with advanced TNM stage

Colorectal cancer (CRC) ranks as the third cause of cancer deaths worldwide [86]. Despite the advances of earlier diagnosis and treatment, a plenty of CRC cases finalized in a very poor prognosis due to the high tendency for tumor invasion and migration of CRC [86-88]. The discovery of novel marker with the underlying action mechanism is worthy of studying for achieving the better diagnosis and treatment of CRC [89].

MiR-124 was down-regulated in CRC progression [90-100]. Compared with paracancerous specimen and normal colorectal cell lines, miR-124 was significantly down-regulated in CRC patients' specimen and tumor cell lines [90-92], as shown in Table-1. MiR-124 expression was negatively correlated with CRC development [96, 98]. In surgical tumorous specimens from CRR patients diagnosed in T3-T4 stages; miR-124 was apparently reduced than the patients in T1-T2 stages [99]. Accordingly, the restored over-expression of miR-124 could reverse the malignant behaviors of CRC tumor cell lines [90, 93-95, 97, 98]. MiR-124 up-regulation by mimic-transfection decreased the *in vitro* 1) proliferation and viability of SW480 and HT29 cells [90], 2) invasion capacity of CT-26 cells [93], and 3) proliferation and migration abilities of LOVO cells [94]. MiR-124 over-expression could enhance the apoptosis of SW480, LOVO [98], HCT116, SW480, HT29 and DLD1 cells [97]. Moreover, miR-124 up-regulation reduced the in vivo growth and invasion of SW620 cells [95], the tumorigenicity and malignancy of CT-26 [89] and SW480 cells [97].

The molecular action mechanism of miR-124 in CRC malignancy was well investigated, as illustrated in Table-1. MiR-124 up-regulation attenuated the *in vitro* malignant properties of SW480 cells through reducing the expression levels of iASPP, PRRX1 [90, 92] and STAT3 [98] and increasing the expression levels of E-cadherin, MGMT, P16 [95] and NF-kB [90]. Consistently, the decreased expressions of PRRX1 [92] and

STAT3 [98] as well as hCLOCK [94] were clearly involved in miR-124-up-regulation-faded *in vitro* malignant behaviors of LOVO, WiDr and COLO201 cells. ROCK1 was consistently reduced following miR-124 up-regulation in SW620, HCT116 and HT29 cells resulting in their decreased *in vitro* malignant behaviors [99, 100]. MiR-124 up-regulation suppressed the *in vitro* malignant properties of SW620 cells *via* down-regulating DNMT3B, SP1 and DNMT1 [95], as well as in DLD-1 and WiDr cells *via* down-regulating DDX6 [96]. Moreover, the restored over-expression of miR-124 decreased the *in vivo* tumor-genesis and aggressiveness of CT-26 cells *via* suppressing the KITENIN, MYH9 and SOX9 expression [93].

MiR-124 down-expression is involved in glioblastoma progression

Glioblastoma (GB) is a fetal malignant brain tumor [101]. It is an uncommon type of malignancy in brain characterized with very invasive conduct and extremely poor prognosis [102]. Like in other types of cancers [103-105], the dysregulation of miRNAs including miR-124 were linked to GB progression [106-109].

As commonly down-regulated and regarded as a tumor suppresser for a variety of cancers, miR-124 deficiency enhanced the clinical progression and development of GB, as well as the proliferative and aggressive behaviors of GB cells [50, 69, 110, 111]. MiR-124 was down-regulated in both GB patients' specimens and GB tumor cell lines [110-112], as summarized in Table-1. Consecutively, the restored over-expression of miR-124 was consistently reported to be able to suppress the *in vitro* proliferation, colony forming, migration and invasion properties of U87 [112-114], U251 [111, 114] and U373 [111] cells, and to augment the apoptosis ofU87 [114] and U251 [110, 111] cells. MiR-124 over-expression also decreased the in vivo tumor growth and malignancy of GB xenograft mouse [115].

MiR-124 functionalizes in GB development and progression mainly through the molecular signaling pathways as summarized in Table-1. By decreasing the expressions of Capn4, vimentin, N-cadherin, p-FAK, MMP2 [113], STAT3 [114] and ROCK1 [112] in U87 cells, and of MAPK14/p38, SERP1 and TEAD1 [115] in U373 and U87 cells, miR-124 up-regulation decreased their malignant behaviors. MiR-124 up-regulation led to the deceased expressions of CDK6 and pSer in both U251 and F6969 cells [110, 111], of STAT3[114], PPP1R13L, MMP-9 and MMP-13 [111] in U251 cells. MiR-124 can bind with the 3'-UTR of PPP1R13L [111]. The down-regulation of miR-124 resulted in increased expression of PPP1R13L, which potentially promoted the malignant behaviors of U251 and U373 cells [111].

MiR-124 deficiency promotes hepatocellular carcinoma progression by increasing TNM stage

Hepatocellular carcinoma (HCC) is the 5th most prevalent and 3rd fatal cancer among cancers [116, 117]. The high frequency of metastasis predicts poor prognosis of HCC [118] patients. The discovery of new indicator or therapeutic target is required for the better diagnosis and treatment of HCC.

MiR-124 deficiency probably benefits HCC development and progression. As summarized in Table-1, up to date, miR-124 was commonly measured down-regulated in HCC patients' specimens and tumor cell lines [119-121].The down-regulation of miR-124 in patients' specimens was reversely correlated with HCC advance [120]. MiR-124 level was significantly reduced in specimens from patients in T3-T4 stage than that of patients in T1-T2 stage [120].

As mentioned above, miR-124 down-regulation promoted the clinical progression of HCC showing its potential tumor suppression effect in HCC. Accordingly, it was confirmed that restored over-expression of miR-124 could suppress the malignant properties of HCC cancer cell [118-121]. Consequentially, the restored over-

expression of miR-124 could decrease the *in vitro* growths of SMC-7721, QGY-7703 [119], MHCC-LM3 [120] and HepG2 [121] cells, migration and invasion abilities of MHCC-LM3 [120], SMMC-7721[118] and QGY-7703 cells [119], motility capacity of SMMC-7721 cells [118]. Increased cell apoptosis induced by MiR-124 up-regulation seemed to contribute in decreased HepG2 proliferation [121]. Furthermore, the tumor suppressing role of miR-124 was validated by *in vivo* experimental evidences [119, 120]. The over-expression of miR-124 in MHCC-LM3 [120], QGY-7703 and SMMC-7721 [119] cells led to their weakened tumorigenicity, tumor formation velocity, size and malignancy in xenograft mice.

The function mechanism of miR-124 in HCC development and progression was investigated by using a variety of HCC cell lines. The deficiency of miR-124 was linked with enhanced malignant properties of HCC cells through promoting the levels of CASC3, STAT3, CD151, PIK3C2A, ROCK2, EZH2, SP1 andintegrin αV [39, 118-121]. MiR-124 over-expression down-regulated CASC3 in MHCC-LM3, Huh7, MHCC-97L and HepG2 cells [120], as well as STAT3 in HepG2 cells [121]. MiR-124 over-expression weakened the malignant properties of QGY-7703 and SMMC-7721 cells through reducing CD151 and PIK3C2A expressions [119], and the malignant behaviors of LM9 cells *via* own regulating ROCK2 and EZH2 [39]. For SMMC-7721 and BEL-7404 cells, miR-124 up-regulation attenuated their malignancy *via* down-regulating Sp1 and integrin αV [118].

CONCLUSION

MiR-124 deregulation is linked to a variety of cancers. Current review showed, up to date, miR-124 deregulation was associated with the development, progression and/or metastasis of breast cancer (BC), nasopharyngeal carcinoma (NPC), bladder cancer (BCa), non-small cell lung cancer (NSCLC), colorectal cancer (CRC), glioblastoma (GB) and hepatocellular carcinoma (HCC). Commonly, the deficiency of miR-124 is negatively correlated with the clinical development and progression BC, NPC, BCa, NSCLC, CRC, GB and HCC patients with advanced TNM stages. Moreover, the reduction of miR-124 enhances the lymph node metastasis of NSCLC and decreases the survival time of BC patients. MiR-124 is also mainly decreased in the tumor cell lines of above cancers. Accordingly, the restored over-expression of miR-124 in cancer cell lines results in their increased *in vitro* apoptosis, their attenuated *in vitro* proliferation, migration, invasion and motility capacities and decreased *in vivo* tumorigenesis and malignancy. MiR-124 mediates the malignant properties of cancer cells through regulating a diversity of gene and protein molecules including STAT3, sp1, CD151, CDK4, NF-kB, MMPs, E-cadherins, AKT1/2, ROCK1/2, Slug, CDH2, LHH2, CD164, LHX2, MYO10, PRRX1, iASPP, SMC4, DNMT3B, Capn4, vimentinand integrin αVet al. in cancer cells, either *via* indirect mediation or direct target binding. Among them, STAT3 activity was most commonly reported to be regulated by the deregulation of miR-124, followed by sp1, CD151, CDK4, NF-kB, MMPs, E-cadherins, AKT1/2 and ROCK1/2. Moreover, miR-124 functions in tumorigenesis through the direct interactions with lncRNAs including MALAT1and NEATI in NPC, and MALAT1 and HOXA11-AS in NSCLC. More interestingly, STAT3and SP1 are involved in the interactions between miR-124 and MALAT1, and between miRR-124 and HOXA11-AS, respectively. In summary, miR-124 plays an important role in tumor cell proliferation, invasion, migration and apoptosis. Its deficiency probably enhances the development and progression of some cancers. It is in potential use as a candidate molecule in understanding the carcinogenesis, diagnosis and treatment of certain cancers.

Conflict of Interest Statement: None declared

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