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The emerging role of microRNA-126 as a potential therapeutic target in cancer: a comprehensive review

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ABSTRACT

MicroRNA-126 (miR-126) has become a key player in the biology of cancer, playing a variety of functions in carcinogenesis and cancer development. The diagnostic and prognostic potential of miR-126 in diverse cancer types is summarized in this thorough analysis, with an emphasis on its role in tumor angiogenesis, invasion, metastasis, cell proliferation, apoptosis, and treatment resistance. MiR-126 dysregulation is linked to a higher risk of developing cancer and a worse prognosis. Notably, miR-126 affects tumor vascularization and development by targeting vascular endothelial growth factor-A (VEGF-A). Through its impact on genes involved in cell adhesion and migration, it also plays a vital part in cancer cell invasion and metastasis. Additionally, miR-126 controls drug resistance, apoptosis, and cell proliferation, which affects cancer cell survival and treatment response. It may be possible to develop innovative therapeutic approaches to stop tumor angiogenesis, invasion, and metastasis, as well as combat drug resistance by focusing on miR-126 or its downstream effectors. The versatility of miR-126's functions highlights the role that it plays in cancer biology. To understand the processes behind miR-126 dysregulation, pinpoint precise targets, and create efficient therapies, more investigation is required. Utilizing miR-126's therapeutic potential might have a significant influence on cancer treatment plans and patient outcomes.

1. Introduction

The neoplastic transformation of normal cells can occur through a series of multistep processes of tumorigenesis, ultimately resulting in malignancy and the initiation of cancer [1,2]. The investigation of the molecular mechanisms underlying the onset and advancement of cancer has emerged as a fundamental aspect of cancer research [3]. This line of inquiry offers a scientific foundation for devising effective approaches to prevent and treat cancer in patients [4]. The dysfunctions of various types of regulators are responsible for alterations in gene expressions that are associated with cancer [5]. Among these regulators, microRNAs (miRNAs) have garnered significant attention in recent decades. The biosynthesis of miRNA entails a multifaceted protein process that involves the participation of various members of the Argonaute protein family, RNA pol II, and the RNase III enzymes (namely, Drosha and Dicer) [6]. Following transcription by RNA polymerase II, the lengthy precursor molecule (pri-miRNA) undergoes processing to yield a secondary transcript featuring a hairpin structure of approximately 70 nucleotides, referred to as the precursor-miRNA (pre-miRNA) [7,8]. Subsequent to its initial formation, the pre-miRNA undergoes further enzymatic modifications facilitated by the ribonuclease Dicer [9]. The occurrence of this cleavage phenomenon leads to the generation of a miRNA duplex that is approximately 22 nucleotides in length and consists of mature miRNA. Subsequently, the mature double-stranded RNA interacts with Argonaute proteins to generate the RNA-induced silencing complex (RISC), which regulates the translation of target mRNA

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containing complementary sequences in the 3′ untranslated region (UTR) [10,11]. miRNAs possess the ability to target a significant proportion of messenger RNAs (mRNAs), thereby conferring upon them crucial regulatory functions in a wide range of physiological and developmental processes. The regulation of gene expression through miRNA is of utmost importance in the cellular response to environmental stressors, including but not limited to starvation, hypoxia, oxidative stress, and DNA damage. This process has been linked to various human diseases, including cancer. The dysregulation of miRNA expression has been found to be closely associated with cancer initiation, progression, and metastasis. It has been observed that a considerable number of miRNAs can function as oncogenes or tumor suppressors [12]. The miRNA-126 (miR-126) holds significant value as a member of the miRNA family. It is encoded by intron 7 of the epidermal growth factor-like domain-containing gene 7 (EGFL7) situated on human chromosome 9q34.3 [13]. Several studies reported on the existence of three distinct EGFL7 isoforms, namely EGFL7 isoforms A, B, and C. These isoforms share the same open reading frame but are transcribed from distinct promoters and employ alternative exons. MiR-126 has the potential to downregulate genes such as mTOR and PIK3R2 at the transcriptional level while also indirectly modulating the expression of EGFL7 isoform B [14–16]. miR-126 exhibits specificity towards endothelial cells and is characterized by its elevated expression levels within the endothelial cell population, including both capillaries and larger blood vessels [17]. Research has demonstrated a clear association between miR-126 and vascular integrity, angiogenesis, as well as various human ailments. According to research, miR-126 has the potential to impede tumor growth by selectively targeting multiple genes, including but not limited to IRS, VEGF, and PI3K. In the case of cancers, miR-126 has been demonstrated to be involved in non-small cell lung cancer (NSCLC) pathogenesis by targeting AKT2 in this cancer [18]. Also, it has been suggested that miR-126 has an inhibitory impact on tumorigenesis in colitis-associated cancer (CAC) by modulating the intercellular communication between intestinal epithelial cells (IECs) and macrophages through CXCL12-IL-6 signaling [19]. The regulation of signaling pathways by miR-126 is a crucial factor in the development of tumors, suggesting that miR-126 may hold promise as a therapeutic target for cancer treatment [20–22]. The present study endeavors to provide a thorough analysis of the importance of miR-126 in the realm of cancer therapy, expounding on its diverse functions in tumor angiogenesis, invasion, metastasis, cell proliferation, apoptosis, and resistance to treatment. Our aim is to offer a thorough comprehension of the potential of miR-126 as a therapeutic target in cancer by integrating the existing knowledge. The objective of this study is to emphasize the diagnostic and prognostic capabilities of the substance in question in different types of cancer. Additionally, we intend to investigate its mechanisms of action in regulating crucial cellular processes and examine its therapeutic implications in hindering tumor angiogenesis, averting invasion and metastasis, encouraging apoptosis, and surmounting treatment resistance. The purpose of this review is to highlight the significance of miR-126 as a potential target for future therapeutic interventions, which could lead to the creation of novel approaches aimed at enhancing the efficacy of cancer treatment.

2. MicroRNA-126 expression in cancer

MiR-126, a miRNA that is specific to endothelial cells, has been implicated in various pathological conditions, including but not limited to diabetes, Parkinson's disease, viral myocarditis, and ischemic stroke. The expression of MiR-126 has been shown to potentially mitigate the progression of diabetes, Parkinson's disease, and ischemic stroke. However, it may also increase the likelihood of viral myocarditis [23,24]. In addition to the aforementioned medical conditions, miR-126 is deemed to be intricately associated with neoplastic growth. The expression of MiR-126 has been observed to be reduced in cancerous cells of various anatomical systems, including the endocrine glands, reproductive system, digestive system, and respiratory system [25–27]. The discovery of MiR-126 was initially made through sequencing in 200, specifically in the heart of the Mus musculus species [28]. According to reports, miR-126 is detectable in high levels in tissues with a high degree of vascularity, such as the heart, liver, and lungs, as well as in cells of the endothelial lineage. This microRNA is known to play important roles in developmental angiogenesis and maintaining vascular integrity [29]. The study conducted by Langraf and colleagues revealed that miR-126 exhibits tissue-specific expression in various bodily systems, including the hematopoietic, respiratory, digestive, and reproductive systems, with a notable presence in the cardiovascular system [30]. According to the research conducted by Harris et al., miR-126 exhibits a significant level of expression in lung and heart tissues that are rich in the endothelium, as well as in primary cultured endothelial cells. However, this expression is not observed in vascular smooth muscle cells and leukocyte cell lines [31]. The gene encoding for MiR-126 is situated within the intron of the EGFL7 gene and is predominantly expressed by endothelial cells. The precursor molecule pre-miR-126 undergoes processing to yield two distinct mature subtypes, namely miR-126–3p, and miR-126–5p. These subtypes are present in significant quantities within endothelial cells. The regulatory function of MiR-126 extends to numerous target genes, and its regulatory network is further influenced by a diverse range of miRNAs. This interplay contributes to the intricate and multifaceted involvement of MiR-126 in various pathological conditions [29,32]. Numerous investigations have documented the downregulation of miR-126 in various cancer categories, suggesting its potential role as a tumor suppressor gene through the inhibition of several oncogenes and signaling pathways [33]. The findings of a study indicated a significant decrease in the expression of miR-126 in glioblastoma samples as compared to the corresponding non-tumoral controls. The findings propose that patients with glioblastoma who exhibit elevated intratumoral miR-126 expression levels experience a noteworthy increase in survival duration compared to those with lower levels of miR-126 [34]. The expression of MiR-126 was found to be decreased in hepatocellular carcinoma tissues in comparison to its expression in noncancerous tissues [35]. The down-regulation of miR-126 in metastatic clear cell renal cell carcinoma (ccRCC) in comparison to primary ccRCC was demonstrated by researchers. The researchers have demonstrated that the expression of miR-126 has the potential to differentiate between subtypes of renal cell carcinoma, specifically clear cell renal cell carcinoma and papillary renal cell carcinoma. An increased level of miR-126 was found to be correlated with a prolonged survival period. The miR-126 molecule exhibited prognostic significance in the subset of patients with larger tumors [36]. A study revealed a notable increase in the expression of ADAM-9, whereas a decrease in the expression of miR-126 is observed in osteosarcoma tumors in humans. The findings of the association analysis indicate that there is a significant involvement of upregulation of ADAM-9 and downregulation of miR-126 in the development of advanced clinical stage and distant metastasis [37]. Additionally, it has been suggested that the expression of miR-126–3p was diminished in cell lines of triple-negative breast cancer (TNBC). The results of functional assays demonstrated that the overexpression of miR-126–3p had an inhibitory effect on various cellular processes, including cell proliferation, migration, invasion, colony formation capacity, and vasculogenesis [38]. Furthermore, it has been observed that miR-126 exhibits an upregulation in endothelial progenitor cells (EPCs). Suppression of miR-126 expression has been found to impede the proliferation, invasion, and migration of EPCs. Additionally, it can hinder the cell cycle and stimulate apoptosis in EPCs [39]. Moreover, it was discovered that the expression of miR-126 was significantly reduced in cases of ovarian cancer. Furthermore, the reduction of miR-126 was found to enhance the aggressive characteristics and predict unfavorable outcomes in individuals with ovarian cancer [40]. It was identified AKT2 kinase as a direct target of miR-126–3p. Ectopic expression and platelet MV-mediated delivery of miR-126–3p downregulated AKT2 expression,

suppressing cell proliferation and invasion in different breast cancer subtypes [41]. Moreover, miR-126–5p could downregulate EZH2, promoting the expression of KLF2 and inhibiting BIRC5 activation. Elevated miR-126–5p enhances the sensitivity of lung adenocarcinoma cells to radiotherapy by inhibiting cell migration, promoting apoptosis, and downregulating BIRC5 via the EZH2/KLF2 axis. These findings suggest that miR-126–5p-mediated regulation of the EZH2/KLF2/BIRC5 axis enhances radiosensitivity in lung adenocarcinoma cells [42]. In ER+ breast cancer (BC), miR-126 is downregulated, and its modulation has been investigated for its role in tumorigenesis. The study showed that miR-126 overexpression significantly reduced proliferation and mammosphere formation in ER+ BC cells, indicating its tumor-suppressive function. In silico analysis identified potential targets of miR-126, including SLC7A5 and PLXNB2, which were downregulated upon miR-126 overexpression. Moreover, high expression of miR-126 or low expression of SLC7A5 correlated with better overall survival in ER+ BC patients [43]. Another study demonstrated that miRNA-126 expression was significantly lower in SW579 cells compared to normal thyroid cells. Overexpression of miRNA-126 in SW579 cells led to decreased cell survival, increased apoptosis, and reduced cell migration. Additionally, the study found that miRNA-126 inhibited the Notch-1/Akt pathway by upregulating intracellular reactive oxygen species. These findings suggest that miRNA-126 plays a role in inhibiting the proliferation and migration of thyroid cancer cells and inducing apoptosis [44].

3. MicroRNA-126 targets and signaling pathways

MicroRNA-126 has been detected in various cancer types such as lung, breast, gastric, colorectal, glioblastoma, bladder, and prostate. Its role in cancer is complex, as it may function as a tumor suppressor by inhibiting oncogenes or as a tumor promoter by inhibiting tumor suppressors (Table 1). A study has uncovered that SOX2 has significant implications in impeding growth by inducing cell cycle arrest and apoptosis. These findings suggest that SOX2 may possess tumor-suppressive properties in cells afflicted with gastric cancer. Otsubo et al. has recently conducted a study wherein they demonstrated the reduction of SOX2 mRNA and protein expression levels in gastric cancer cell lines due to the downregulation of miR-126. Furthermore, it was discovered that the expression of miR-126 exhibited an inverse correlation with the expression of SOX2 in specific cultured and primary gastric cancer cells that lacked DNA methylation of SOX2. This suggests that the anomalous expression of miR-126 may serve as a new mechanism for the down-regulation of SOX2 in gastric cancer. In addition, the over-expression of pre-miR-126 was found to enhance the growth of gastric cancer cells in both anchorage-dependent and -independent manners in vitro. Moreover, it was observed to elevate the expression of oncogenic PLAC1 in a cell line of gastric cancer. The results of this study indicate that miR-126 may possess oncogenic properties and regulate the expression of SOX2 in cells affected by gastric cancer [45]. The study conducted by Ichikawa et al. aimed to examine the impact of enforced miR-126–3p expression on various cellular processes such as proliferation, migration, invasion, apoptosis, and protein expression in HeLa, a cervical cancer cell line. The HeLa cells were transfected with miR-126–3p miRNA, and subsequent analysis revealed a significant reduction in proliferation, migration, and invasion as determined by cell counting, wound healing, and cell migration and invasion assays. These findings were in contrast to the results obtained from cells transfected with a negative control mimic. The transfection of miR-126–3p resulted in decreased levels of phosphoinositide 3 kinase (PI3K), phosphorylated 3-phosphoinositide-dependent protein kinase-1 (p-PDK1), and p-AKT proteins in the cells. The downregulation of phosphorylated 70S6K (p-p70S6K), phosphorylated glycogen synthase kinase 3β (p-GSK3β), phosphorylated S6K (p-S6K), cyclin D1, phosphorylated p21-activated kinase 1 (p-PAK1), Rho-associated coiled-coil containing protein kinase 1 (ROCK1), myotonic dystrophy-related CDC42-binding kinases α (MRCKα) and phospholipase C γ1 (p-PLCγ1) was observed. This observation implies that miR-126–3p has the potential to inhibit downstream effectors of the PI3K/PDK1/AKT pathway [46]. The upregulation of microRNA-126 in cell lines of non-small cell lung cancer (NSCLC) resulted in a reduction in cellular proliferation in vitro and a decrease in tumor growth in the xenograft model of nude mice. The repression of PI3K-Akt pathway activity was achieved by microRNA-126 through the targeting of binding sites located in the 3′-untranslated region of PI3KR2 mRNA. The NSCLC lines and tumor tissues exhibited a reduction in the expression level of microRNA-126. The study findings indicate that patients exhibiting low levels of microRNA-126 expression experienced notably reduced survival time compared to those with high microRNA-126 expression [47]. Research has shown that an elevated expression of miR-126–5p/3p in cases of acute myeloid leukemia is associated with an unfavorable prognosis. In addition, it was observed that miR-126–5p facilitated resistance to cytarabine through the augmentation of Akt phosphorylation [48]. The role of miR-126 in invasion was identified by Jia et al. due to its capacity to target ADAM9. A noteworthy observation was made regarding the expression of miR-126 and ADAM9 in muscle-invasive bladder cancer cells, indicating a significant inverse correlation between the two. It was found that ADAM9 was upregulated in these cells. The invasiveness of cells exhibiting low miR-126 levels was found to be reduced upon knockdown of ADAM9, whereas experimental overexpression of ADAM9 reproduced the invasive phenotype. Moreover, the evaluation of ADAM9 expression through immunohistochemistry demonstrated a significant association with unfavorable prognosis among individuals diagnosed with urothelial carcinoma. The findings of their research indicate that miR-126 plays a crucial role in suppressing tumor growth by targeting ADAM9, thereby impeding cellular invasion [49]. A study revealed a significant correlation between diminished miR-126 expression and heightened CXCR4 expression, and the resultant poor prognosis of individuals suffering from colorectal cancer (CRC). Additionally, a negative correlation was observed between the expression of miR-126 and CXCR4 in CRC specimens, suggesting the involvement of a post-transcriptional regulatory mechanism. The study has disclosed that miR-126 has the potential to serve as a standalone prognostic determinant in CRC. The crucial involvement of SDF-1/CXCR4 signaling in cellular adhesion, migration,

Table 1
miR-126 and its targets in various cancers.

Type of cancer	Target	Mechanism	Reference
Gastric cancer	SOX2	Targets downstream pro-oncogenic target genes of SOX2, such as PLAC1, and contributes to gastric carcinogenesis.	[45]
Cervical cancer	PDK1	inhibits cell migration and invasion and induces apoptosis by regulating the PI3K/PDK1/AKT pathway	[46]
NSCLC	PI3KR2	Inhibits tumor cell growth	[47]
Acute myeloid leukemia	Klotho	Results in a decrease in the sensitivity to cytarabine	[48]
Bladder cancer	ADAM9	Inhibits cell invasion	[49]
Colorectal cancer	CXCR4	Decreases distant metastasis, clinical TNM stage, and poor survival	[50]
Prostate cancer	ADAM9	Serves a role in the proliferation and metastasis	[51]
Cervical cancer	ZEB1	Inhibits the proliferation, migration and invasion by suppressing MMP2, MMP9 expression and inactivating JAK2/STAT3 signaling pathway	[52]
Lung cancer	LAT1	Inhibits cell proliferation and angiogenesis, with subsequent inhibition of mTOR signaling	[53]
Colorectal cancer	IRS-1	Suppresses AKT and ERK1/2 activation, proliferation, migration, and invasion and causes cell cycle arrest	[54]
NSCLC	VEGFA	Increases the sensitivity of cells to anticancer agents through negative regulation of a VEGF/PI3K/Akt/MRP1 signaling pathway	[55]

and metastasis underscores the plausible correlation between reduced levels of miR-126 and the gravity of the ailment in CRC sufferers. This association can be attributed to the conceivable control of CXCR4 expression by miR-126 [50]. The findings of another study indicated a notable reduction in miR-126 expression within both prostate cancer (PCa) tissues and cell lines. In vitro, experiments have shown that overexpression of miR-126 can lead to a reduction in prostate cancer cell proliferation and metastasis, as well as a reversal of the epithelial-mesenchymal transition process. Furthermore, ADAM9, which is the intended gene of miR-126, was observed to be upregulated, thereby restoring various cellular processes such as proliferation, migration, and invasion. Patients who demonstrated elevated levels of ADAM9 expression manifested a reduced duration of biochemical recurrence-free survival [51]. The expression of miR-126 was found to be decreased in both cervical cancer tissues and cells. Furthermore, the overexpression of miR-126 resulted in the downregulation of ZEB1. The upregulation of miR-126 resulted in the targeting of ZEB1, leading to the suppression of MMP2 and MMP9 expression, as well as the deactivation of the JAK2/STAT3 signaling pathway. This ultimately resulted in the inhibition of in vitro proliferation, migration, and invasion [52]. The transfection of miR-126 mimics and antisense inhibitors was utilized to achieve overexpression and knockdown of miR-126 in primary human lung microvascular endothelial cells (HLMVEC). Elevating miR-126 expression in HLMVEC resulted in a decrease in cellular proliferation, attenuation of tube formation, and an increase in cellular apoptosis. Conversely, reducing miR-126 expression promoted cellular proliferation and tube formation. The transcriptomic profile was found to be proapoptotic and antiangiogenic in association with miR-126 through the use of whole-genome RNA sequencing. Through the implementation of validation assays and knockdown methodologies, it has been determined that the impact of miR-126 on angiogenesis in HLMVECs is facilitated by the LAT1 (L-type amino acid transporter 1), which operates through the regulation of mTOR signaling [53]. In their study, Zhou et al. have reported that miR-126 targets the 3′-UTR of IRS-1 and that this interaction leads to the functional downstream regulation of IRS-1. The expression of IRS-1 was inhibited by both endogenous miR-126 and exogenous miR-126 mimics. In addition, studies involving gain-of-function or loss-of-function techniques have demonstrated that the upregulation of miR-126 results in the downregulation of IRS-1, inhibition of AKT and ERK1/2 activation, suppression of proliferation, migration, and invasion of colorectal cancer cells, and induction of cell cycle arrest. However, no significant impact on cell apoptosis was observed. The downregulation of miR-126 facilitated the aforementioned cellular processes in HCT-116 cells. Furthermore, it led to the activation of AKT and ERK1/2 via the upregulation of IRS-1 protein expression. The potential involvement of MiR-126 in the modulation of the biological behavior of CRC cells has been suggested. This may occur, at least in part, through the targeting of IRS-1 via AKT and ERK1/2 signaling pathways [54]. Furthermore, it has been documented for the initial instance that miR-126 played a role in controlling the reaction of NSCLC cells to chemotherapy for cancer treatment. Upon transfecting A549 cells with miR-126 mimic or inhibitor, it was observed that an augmented expression of miR-126 was significantly correlated with a reduced half maximal inhibitory concentration of adriamycin (ADM), and vincristine, an escalated accumulation of ADM, a down-regulation of vascular endothelial growth factor A (VEGFA) and multidrug resistance-associated protein 1 (MRP1), and inactivation of the Akt signaling pathway. In addition, the upregulation of miR-126 resulted in the inhibition of A549 xenograft growth and downregulation of VEGFA and MRP1 expression. The interaction between miR-126 and the 3′-untranslated region of VEGFA led to a significant down-regulation of VEGFA expression. However, the suppression of MRP1 by miR-126 was only partially attenuated upon restoration of VEGFA. The study found that the upregulation of miR-126 in NSCLC cells resulted in increased sensitivity to anticancer agents. This effect was found to be negatively regulated by the VEGF/PI3K/Akt/MRP1 signaling pathway. The inhibitor LY294002, which targets the PI3K/Akt pathway, was observed to reduce this effect [55]. In vitro, it was observed that miR-126 impeded the formation of tubes in HUVECs through its interaction with the EGFL7 gene, leading to a reduction in EGFL7 expression. Additionally, the PI3K/AKT signaling pathway was down-regulated. The administration of atorvastatin resulted in an augmentation of tube formation in traumatic brain injury (TBI) rat models, which was attributed to the up-regulation of PI3K/AKT signaling pathway and an increase in EGFL7 expression [56]. Moreover, the ectopic upregulation of miR-126 exhibited inhibitory effects on the proliferation, invasion, and migration of ovarian cancer cells. It is plausible that miR-126 may impede the metastasis and growth of ovarian cancer tumors through the modulation of the ERK/MAPK signaling pathway and EMT. The study has identified EGFL7 as a potential target of miR-126, which negatively regulates the former and provides to the progression of ovarian cancer. This suggests that miR-126 may act as a tumor suppressor for ovarian cancer by targeting EGFL7 [40].

4. Clinical significance of microRNA-126 in cancer

The non-coding RNA known as miR-126 has been identified as a noteworthy entity with potential diagnostic and prognostic value in the context of cancer. The anomalous manifestation of miR-126 has been detected in diverse categories of cancer, and its irregularity has been associated with the commencement, advancement, metastasis, and reaction to the treatment of tumors. This section will examine the diagnostic and prognostic implications of miR-126 in cancer, as well as its underlying molecular mechanisms.

The findings of a study indicated a significant correlation between reduced miR-126 expression and the advancement of oral squamous cell carcinoma (OSCC), as well as the presence of nodal metastasis, increased vessel density, and unfavorable prognosis [57]. The expression levels of miR-126 were found to be lower in glioblastoma tumor tissues as compared to the adjacent non-tumor brain tissues. It was observed that patients who exhibited elevated intratumoral miR-126 expression had a considerably enhanced duration of survival, suggesting that a reduced downregulation of miR-126 could be linked to a more favorable prognosis [34]. A new study reveals that in cases of CRC, a decrease in miR-126 expression and an increase in CXCR4 protein expression are linked to the occurrence of distant metastasis, advanced clinical stage, and unfavorable overall survival. Furthermore, miR-126 has been recognized as a self-reliant prognostic determinant in patients with CRC [50]. The diagnostic and prognostic efficacy of miR-126 in NSCLC is a topic of debate in the academic literature. A meta-analysis was performed to investigate the expression of miR-126 and its potential diagnostic and prognostic significance in NSCLC. The meta-analysis encompassed a total of thirteen studies, and the collective findings revealed that miR-126 exhibited a moderate level of diagnostic efficacy for NSCLC, as evidenced by a combined sensitivity of 0.83 and specificity of 0.83. The analysis of prognostic factors indicated that reduced levels of miR-126 were linked to unfavorable outcomes in terms of overall survival, with a hazard ratio of 0.79. The results of this study indicate that miR-126 has the potential to function as a diagnostic biomarker and prognostic indicator for NSCLC [58]. The latest investigation assessed the expression of miR-126 in tumor tissue obtained from a cohort of 452 patients diagnosed with colon cancer. The findings of the analysis indicated that a significant correlation existed between elevated expression levels of miR-126 in both tumor cells and adjacent tumor stroma and enhanced disease-specific survival. The results of the multivariate analysis indicated that elevated levels of miR-126 expression in neoplastic cells were a significant and autonomous prognostic factor for improved outcomes, particularly in individuals with stage II colon cancer. The results indicate that miR-126 has the potential to serve as a favorable prognostic indicator in colon cancer patients with stage I-III, enabling the identification of those who could derive therapeutic benefits from adjuvant chemotherapy [59]. Patients diagnosed with

esophageal adenocarcinoma (EAC) and exhibiting elevated levels of miR-126 expression demonstrated unfavorable survival outcomes. The functional assays conducted on EAC cell lines revealed that modulation of miR-126 expression had discernible effects on genes associated with cell death, DNA repair, and the secretion of angiogenic and pro-inflammatory factors. Moreover, miR-126 was found to modulate the viability of tumor cells and the expression of genes associated with both pro- and anti-apoptotic pathways. Elevated miR-126 expression in pre-treatment tumors of patients was found to be significantly correlated with unfavorable survival outcomes, regardless of ypN-stage. The aforementioned discoveries underscore the significance of miR-126 as a plausible prognostic biomarker and therapeutic objective in EAC [60]. The expression of miR-126–5p was observed to be notably reduced in cases of acute promyelocytic leukemia (APL) in comparison to non-APL cases. The miR-126–5p expression levels exhibited a correlation with distinct clinical parameters and complete remission. Additionally, these factors were recognized as prognostic indicators in patients with APL [61]. The incidence and advancement of lung squamous cell carcinoma (LUSC) have been linked to reduced expression of miRNA-126–3p. In accordance with prior research, the present study has also observed diminished levels of miRNA-126–3p expression in LUSC specimens. The results of the functional analysis indicate that the target genes of miRNA-126–3p participate in biological processes that facilitate the progression of LUSC. The potential of miRNA-126–3p as a biomarker for early diagnosis and prognosis of LUSC is suggested by its down-regulation [62].

The potential of miR-126 as a diagnostic biomarker has been demonstrated in various types of cancer. The deregulation of miR-126 expression has been linked to distinct tumor characteristics, indicating its potential as a biomarker for the timely identification and differentiation of malignant tumors from benign lesions. Liu and colleagues conducted an investigation into the prognostic significance of miR-126 in the context of epithelial ovarian cancer (EOC). The findings indicate that the expression of miR-126 was comparatively reduced in EOC tissues, specifically in omental metastases, in contrast to normal tissues. Remarkably, individuals with increased miR-126 expression manifested unfavorable outcomes in terms of both overall survival and relapse-free survival. The results of the multivariate analysis revealed that miR-126 could be considered an autonomous prognostic determinant for unfavorable relapse-free survival in EOC, thus highlighting its potential as a biomarker for anticipating recurrence [63]. Furthermore, an additional research endeavor examined microRNAs present in extracellular vesicles found in urine as plausible biomarkers for the detection of prostate cancer. The study revealed that miR-126–3p was observed to be upregulated in urinary extracellular vesicles (EVs) of patients with PCa in comparison to those who were negative for biopsy. The results of logistic regression analysis revealed a significant association between this particular microRNA and the ability to predict the presence of prostate cancer in biopsy specimens. The results indicate that miR-126–3p exhibits superior sensitivity and specificity values compared to serum prostate-specific antigen (PSA), thereby highlighting its potential as a biomarker for PCa [64].

MicroRNAs (miRNAs) have gained significant attention in the field of cancer research and therapeutic advancements, particularly in relation to miR-126. There exist multiple prospective domains for further exploration and therapeutic advancement of miRNAs in the context of cancer therapy. Initially, additional investigation is required to clarify the mechanistic function of miR-126 in diverse forms of malignancy. Gaining comprehension of the precise targets and subsequent signaling pathways impacted by the dysregulation of miR-126 would yield valuable insights into the affected processes and pathways. Subsequently, it is imperative to conduct comprehensive research to ascertain the diagnostic efficacy of miR-126 across various types of cancer. It is imperative to conduct extensive clinical trials and validation studies to evaluate the diagnostic biomarker's sensitivity, specificity, and accuracy on a large scale. The investigation of its capacity as a non-invasive liquid biopsy biomarker has the potential to transform the methods of cancer diagnosis and surveillance. Thirdly, comprehensive research is necessary to clarify the prognostic significance of miR-126 in different types of cancer. Research endeavors should strive to establish the correlation between the study in question and clinical outcomes, including but not limited to survival rates, recurrence rates, metastasis rates, and treatment response rates. The comprehension of the prognostic implications associated with the dysregulation of miR-126 would facilitate personalized treatment decisions and patient management. Furthermore, it is recommended that research endeavors be directed toward the advancement of therapeutic approaches based on miR-126. One potential approach is the manipulation of miR-126 expression levels in cancer cells through replacement or inhibition. The examination of miR-126's therapeutic potential can be facilitated through preclinical investigations utilizing in vitro and in vivo models. These studies can offer significant knowledge regarding the impact of miR-126 on tumor growth, angiogenesis, metastasis, and its susceptibility to chemotherapy or targeted agents. Furthermore, exploring the potential synergies resulting from the integration of miR-126-based interventions with established therapeutic approaches such as chemotherapy, immunotherapy, or targeted therapy represents a promising direction for forthcoming investigations. The utilization of combinatorial strategies has the potential to augment the effectiveness of treatments, surmount drug resistance, and enhance patient prognoses. In addition, the development of delivery systems that are both efficient and targeted for miRNA-based therapeutics is of utmost importance. The successful clinical translation of miR-126-based therapies necessitates the implementation of strategies aimed at improving stability, enhancing cellular uptake, and achieving specific tissue or tumor targeting. Finally, the incorporation of miR-126 expression and other pertinent biomarkers into treatment decision-making algorithms can expedite the implementation of personalized medicine strategies. The identification of patients who are likely to benefit from miR-126-based therapies and the optimization of treatment strategies based on individual miRNA profiles may lead to improved treatment outcomes.

5. Target prediction and gene ontology (GO) of targets

In this study, we utilized miRWalk v.3 [65], a widely used bioinformatics tool, to predict the targets of miR-126-3p and miR-126–5p. The analysis revealed a total of 270 predicted targets for miR-126-3p and 72 targets for miR-126–5p (Fig. 1). To gain insights into the potential functional roles of these predicted targets, we performed GO analysis. The GO analysis provides a systematic way to annotate genes and their associated biological processes, cellular components, and molecular functions (Fig. 2). The GO analysis of the targets for miR-126-3p and miR-126-5p allowed us to categorize these genes based on their functional characteristics. The analysis provided valuable information about the potential biological processes and molecular functions that these miRNAs may be involved in. EnrichR online tool was used to perform GO analysis [66].

In terms of biological processes, the analysis identified enriched categories that suggest the involvement of miR-126-3p and miR-126-5p targets in the regulation of germinal center formation and the regulation of hydrolase activity. These findings imply that these miRNAs may play important roles in modulating these cellular processes, which are crucial for immune responses, protein degradation, and other essential biological functions. Regarding cellular components, the GO analysis highlighted specific subcellular locations where the targets of miR-126-3p and miR-126-5p are active, such as the early endosome and early endosome membrane. The enrichment in these compartments suggests that miR-126-3p and miR-126-5p may participate in regulating processes associated with vesicular trafficking, intracellular sorting, and membrane dynamics. Furthermore, the analysis of molecular functions associated with the predicted targets revealed interesting insights into the biochemical activities and interactions mediated by miR-126-3p and

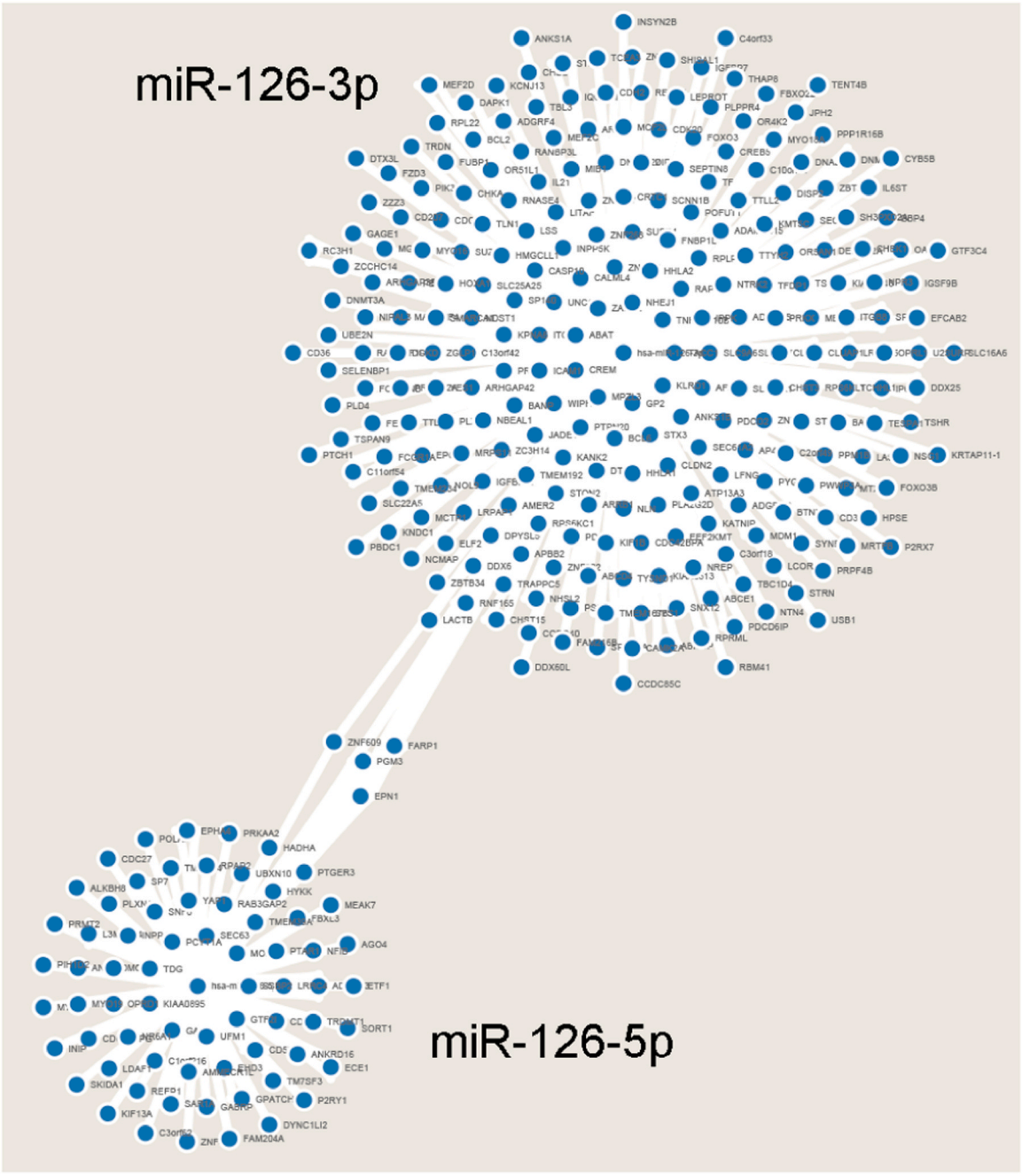

Fig. 1. Network of Predicted Targets of miR-126-3p and miR-126-5p. The figure illustrates the network of predicted targets for miR-126-3p and miR-126-5p, generated using bioinformatics analysis. Each node represents a target gene, and the edges depict the potential regulatory relationships between the miRNAs and their targets.

miR-126-5p. Specifically, the enriched molecular functions included DNA-methyltransferase activity and tRNA methyltransferase activity. These findings suggest that these miRNAs may be involved in epigenetic regulation and post-transcriptional modifications of gene expression, highlighting their potential impact on cellular processes. Overall, the GO analysis of the predicted targets of miR-126-3p and miR-126-5p provides valuable information about the potential roles of these miRNAs in regulating important biological processes, their subcellular localization, and the molecular functions of their targets. These results open up new avenues for further experimental investigations to validate the functional relevance of miR-126-3p and miR-126-5p and their targets in the context of cancer.

6. Conclusion

The potential of miR-126 as a target for cancer diagnosis and therapy has been identified. The biomarker in question exhibits promise for evaluating cancer risk, specifically in relation to BRCA1 promoter methylation in breast and ovarian cancers. The study reveals that heightened miR-126 expression in peripheral white blood cells is correlated with a reduced likelihood of distant metastasis in breast cancer. However, in ovarian cancer, augmented miR-126 expression is unexpectedly associated with disease advancement and inferior overall survival. The results highlight the intricate and situational character of miR-126's involvement in the advancement of cancer. The potential therapeutic implications of miR-126 are noteworthy, given its

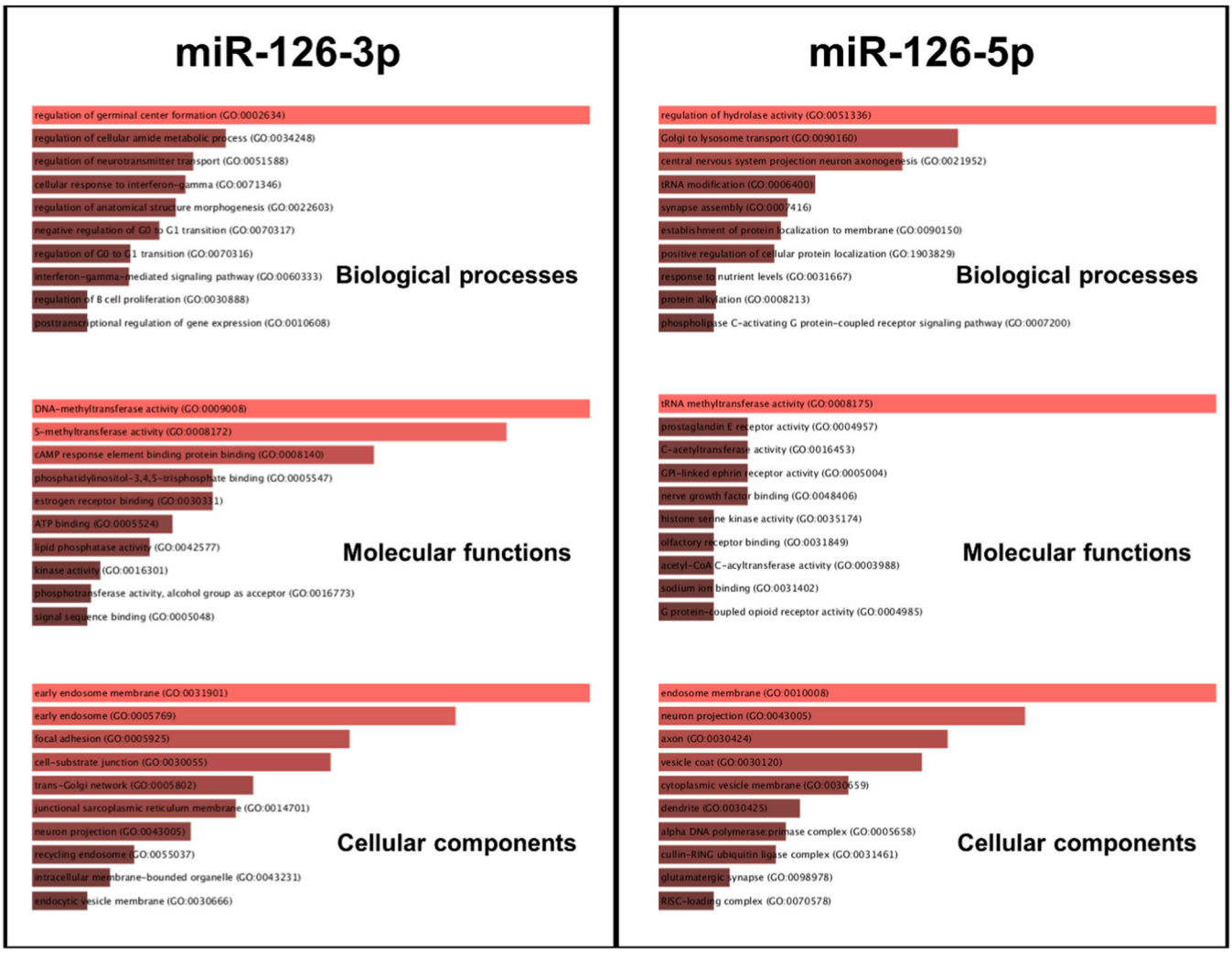

Fig. 2. Bar Graphs of GO Analysis Results. The figure presents the results of the GO analysis conducted using the EnrichR online tool. The bar graphs depict the enriched GO categories associated with the predicted targets of miR-126–3p and miR-126–5p. The y-axis represents the GO categories, while the x-axis represents the significance level. Each bar represents a specific GO category, and its height reflects the degree of enrichment or significance.

involvement in the regulation of cancer angiogenesis and invasion. Nevertheless, additional investigation is required to comprehensively comprehend the functional implications and regulatory mechanisms of the aforementioned phenomenon in cancer cells. Furthermore, through bioinformatics analysis, a plethora of potential targets for miR-126-3p and miR-126-5p have been identified, offering valuable insights into the cellular components, biological processes, and molecular functions that may be impacted by miR-126. In general, miR-126 exhibits potential as a promising area for further exploration and therapeutic advancement in the field of oncology. Additional research is necessary to clarify the exact mechanisms of action, discover more target genes, and investigate the potential of this substance as a therapeutic intervention or diagnostic tool. The complex relationship between miR-126 and the advancement of cancer underscores the necessity for a thorough comprehension of its function in various types of cancer, ultimately facilitating the development of individualized therapeutic approaches and enhancing patient results.

Code availability

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CRediT authorship contribution statement

Abduladheem Turki Jalil: Supervision, Conceptualization, Writing – original draft. **Mohanad Ali Abdulhadi and Lubna R. Al-Ameer**: Data curation, Writing – review & editing. **Rahman S. Zabibah and Hussein Abdullah Abbas:** Data curation, Writing – review & editing. **Ali A. Fadhil and Muna S. Merza:** Writing – review & editing. All authors have read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Not applicable.

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