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REVIEW ARTICLE

miR-106b as an emerging therapeutic target in cancer

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Abstract MicroRNAs (miRNAs) comprise short non-coding RNAs that function in regulating the expression of tumor suppressors or oncogenes and modulate oncogenic signaling pathways in cancer. miRNAs expression alters significantly in several tumor tissues and cancer cell lines. For example, miR-106b functions as an oncogene and increases in multiple cancers. The miR-106b directly targets genes involved in tumorigenesis, proliferation, invasion, migration, and metastases. This review has focused on the miR-106b function and its downstream target in different cancers and provide perspective into how miR-106 regulates cancer cell proliferation, migration, invasion, and metastases by regulating the tumor suppressor genes. Since miRNAs-based therapies are currently being developed to enhance cancer therapy outcomes, miR-106b could be an attractive and prospective candidate in different cancer types for detection, diagnosis, and prognosis assessment in the tumor.

Introduction

MicroRNAs (miRNAs) consists of short non-coding RNAs that control several gene expression. Recently, miRNAs have appeared as a potential molecular therapeutic approach for different diseases such as cancer.[1] In cancer cells, the aberrant miRNAs expression has been observed in different cancer and affects the hallmarks for tumor initiation and progression. Several miRNAs play essential roles in the resistance of malignant cells to many anti-cancer agents.[2,3] Most miRNAs are transcribed into primary miRNAs from DNA sequences and then processed into precursor miRNAs and mature miRNAs. Furthermore, miRNAs have been shown to bind with the target mRNAs to regulate the several genes involved in disease progression and cell death pathways.[4] miRNAs behave either as a tumor suppressor or oncogene based on their targets.[5]

miR-106b overexpression has been stated in multiple tumor types and controls cell proliferation, migration, invasion, and metastases. Aberrant miR-106b expression is linked with breast cancer (BCa), prostate cancer (PCa),

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lung cancer, gastric cancer (GC), colorectal cancer (CRC), hepatocellular carcinoma (HCC), and esophageal squamous cell carcinoma (ESCC). miR-106b and its seed family member like miR-106b-5p shows oncogenic properties and regulates different signaling pathways by targeting different genes involved in tumor initiation and progression and contributes to resistance against anti-cancer therapies.[6,7] As its oncogenic role, several potential targets, like PTEN/AKT, La related protein 4B (LARP4B), Calponin 1, Runt-related transcription factor 3 (RUNX3), Disabled homolog 2 (DAB2), Deleted in liver cancer-1 (DLC-1), FOG2, RE-1 Silencing Transcription Factor (REST-1), Fucosyltransferase 6 (FUT6), Arm protein lost in epithelial cancers, on chromosome X (ALEX1) and BTG anti-proliferation factor 3 (BTG3) have been confirmed for their involvement in cancer initiation and progression through multiple pathways.

Moreover, miR-106b overexpression is associated with aggressive clinicopathological features. Experimental findings have shown that miR-106b could be an attractive and potential biomarker in different types of cancers for detection and prognosis assessment of the tumor. Clinical findings have reported that specific alteration in tumors in miRNAs plasma/serum of cancer patients has exhibited the plasma circulating miRNAs to be the new noninvasive biomarkers in various cancer patients.[8] In the past decade, the importance of microRNAs (miRNAs) in cancer therapeutics have been progressively acknowledged. Particularly, miRNAs had been lately proven to reverse the resistance to chemotherapy drugs such as Doxorubicin, Cisplatin, and 5-fluorouracil.[9]

This review provides a brief overview of miR106b-mediated signaling pathways in different cancer types and focuses on the expression and targets of miR106 family members in cancer tissue or cells. The article further explores the possibilities of exploring the roles of this miRNA for diagnostic and prognostic purposes in cancer therapeutics.

miRNA biogenesis: mechanism and important players

The synthesis of miRNA is a multi-step process in which primary (pri-miRNA) is transcribed from the Mini-chromosome Maintenance Complex Component 7 (*MCM7*) gene by RNA polymerase.[10–12] In some cases, miRNAs are transcribed as one lengthy transcript known as clusters, which may have similar seed regions. In such cases, these are considered as a family.[13] Further, miRNA biogenesis includes cleavage events, one in the nucleus and another in the cytoplasm performed by RNase III family members, Drosha in the nucleus, and Dicer in the cytoplasm.[14] The processing and cleavage of pri-miRNA are performed by a complex of Drosha/DGCR8 (*Di*G*eo*rge syndrome *c*ritical *re*gion 8) to release the intermediate pre-miRNA. It binds to Exp5/Ran-GTP complex and gets exported to the cytoplasm. The processing of pri-miRNA depends on the structural characteristics of distinct pri-miRNA sequences.[15] Next, pre-miRNA is digested by Dicer into a mature duplex (miRNA/miRNA*), where miRNA* represents a passenger strand.

Under normal circumstances, one strand from the duplex is recruited into the miRNA-induced silencing complex (miRISC) and functions as a guide for miRNA to recognize the mRNA targets and guide for translational repression, deadenylation, and degradation while another passenger strand is degraded. During this process, proteins like Argonaute and glycine—tryptophan protein 182 kDa (GW182) interact with miRNAs. The resultant RISC complex binds to the mRNA's 3′untranslated regions and plays a crucial role in miRNA-mediated mRNA degradation and translational repression[16,17] (Fig. 1). The miRNA mediated gene regulation depends on the extent of the complementary pairing of miRNA and sequence of target mRNA. The partial homology between miRNA:mRNA target sequences lead to translation repression; however, a perfect homology may result in mRNA degradation.[17,18]

miR-106b family members

The miR-106b family members -miR-106a/b, 17-5p, 20a/b, and 93, are overexpressed in multiple cancer and involves in cell cycle regulation and functioning of the checkpoint and promote cell cycle progression.[19] miR-106b with miR-93 and -25 forms a cluster of miR-106b-25[20–22] (Fig. 2). miR-106b-25 cluster is situated in the intron region of MCM7 gene,[23] which is important for DNA replication initiation.[24] miR-106b-25 cluster has been reported to be overexpressed in multiple cancers, including HCC,[22] esophageal adenocarcinoma,[25] BCa,[26] and prostate cancer.[22,23,27] This cluster has been demonstrated as pro-oncogenic and shown to play a role in proliferation, anti-apoptotic, and cell cycle progression by regulating TGF-β.[28] Similar to miR-106b, miR-106b-5p transcribed from the cluster of miR-106b-25 is also reported as oncogene in BCa,[29–31] GC,[32] HCC.[7,33,34] miR-106-5p function like other miRNAs by complementary pairing to specific mRNAs to degrade/suppress translation of targeted mRNA -promoting or -suppressing genes. Several targets of miR-106-5p have been reported in human cancer and play a major role in proliferation, migration, invasion, and cell cycle.[35]

Regulation of miR-106b

Studies demonstrated that the miR-106b cluster is situated in the *MCM7* gene.[23] Aberrant expression of MCM7 is seen in several human cancer[36] and correlated with the miR-106b cluster expression.[37] The transcription factor E2F has been shown to regulate the miR-106b cluster in several cancers. It has been reported that E2Fs have several transcriptional sites in MCM7 promotor and directly regulate a few miRNAs cluster and in turn control E2F expression.[38,39] Thangavel et al reported that MCM7 is mainly regulated by Retinoblastoma (RB) through binding of the proximal E2F element in the promoter in breast cancer model[40] and suggested the miR-106b cluster repression through the RB/E2F pathway. However, the MCM7 promoter also possesses an E-box binding site for the MYC.[39] Another study also showed that *MYC* oncogene regulates both the miR-106b-25 cluster and MCM7 via E2Fs. The family of *MYC* oncogene, including *MYC*, *MYCL*, and *MYCN*, play major functions in tumor development and progression and therapeutic

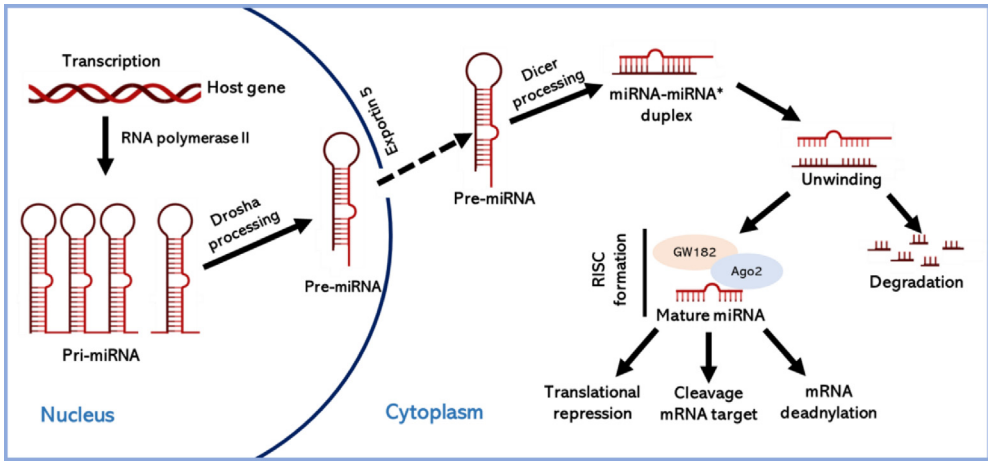

Figure 1 A schematic of miRNAs biogenesis. miRNA biogenesis begins in the nucleus, where genes are transcribed to a primary miRNA (pri-miRNA) by RNA polymerase II. The pri-miRNA is processed and cleaved by Drosha/DGCR8 complex to release the intermediate pre-miRNA. It binds to Exp5/Ran-GTP complex and gets exported to the cytoplasm. Next, pre-miRNA is digested by Dicer into a mature duplex (miRNA/miRNA*), where miRNA* represents as a passenger strand. One strand of this duplex is loaded into the miRNA-induced silencing complex (miRISC) and functions as a guide for miRNA to recognize the mRNA targets and induce their translational repression deadenylation and degradation while another passenger strand is degraded. During this process, proteins like Argonaute and glycine—tryptophan protein 182 kDa (GW182) interacts with miRNAs. The resultant RISC complex binds to the mRNA's 3′untranslated regions and plays a crucial role in miRNA-mediated mRNA degradation and translational repression.

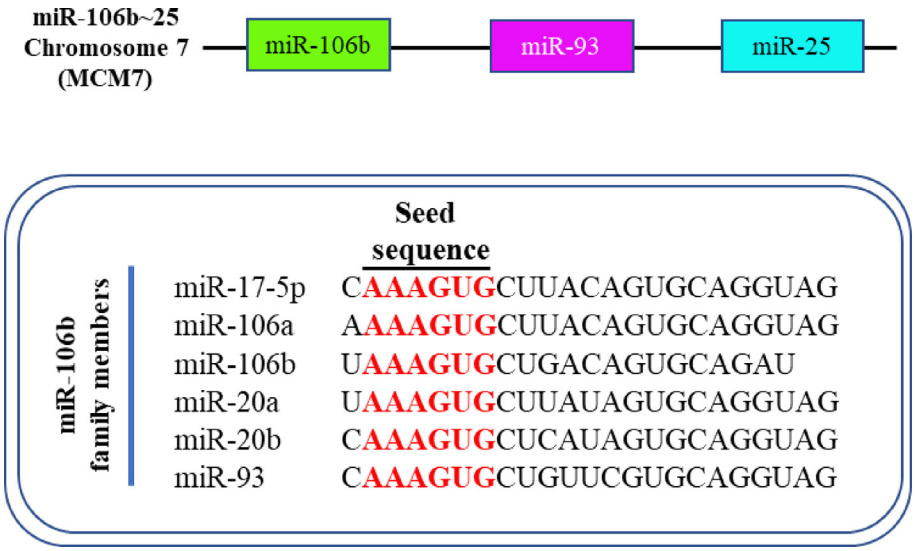

Figure 2 A schematic illustration of the miR-106b~25 clusters. The genomic structure of the miR-106b~25 cluster on chromosome 7. Sequences of the miR-106b family members and conserved seed sequences among the family members are highlighted with blue color.

resistance.[41] MYC activates transcription factors E2F1 and E2F3, which leads to increase MCM7 and miR-106b-25 clusters. In turn, E2F expression is downregulated by miR-106b and miR-93 through E2F1 transcript through negative feedback loop[42,43] (Fig. 3).

MCM7 is also directly regulated by MYC family member-MYCN.[44] MYCN role has been reported in prostate neuroendocrine differentiation and frequently amplified in neuroblastoma.[45,46] This report suggests that MYCN activates the MCM7 promoter through direct interaction.[44] Recently, bromodomain-containing protein 4 (BRD4) has been identified in the regulation of miR-106-5p transcription through E2F[32]. In this study, BRD4 was found to be recruited to the promoter of miR-106b-5p with the help of E2F and aided miR-106b-5p transcription. In addition, BRD4 negatively regulates c-MYC stability and is involved in the cell cycle, inflammatory cytokines, and cancer development.[32,47] Gong et al demonstrated the role of the transforming growth factor-beta (TGF-β) in miRNA regulation. The dual nature of TGF-β has been reported in many cancers, either as a tumor suppressor or tumor promoter. TGF-β upregulates transcription of miR-106b, independent of the promoter of the *MCM7* gene by c-jun activation.[48] Hippo signaling pathway co-activator YAP/TAZ is known to

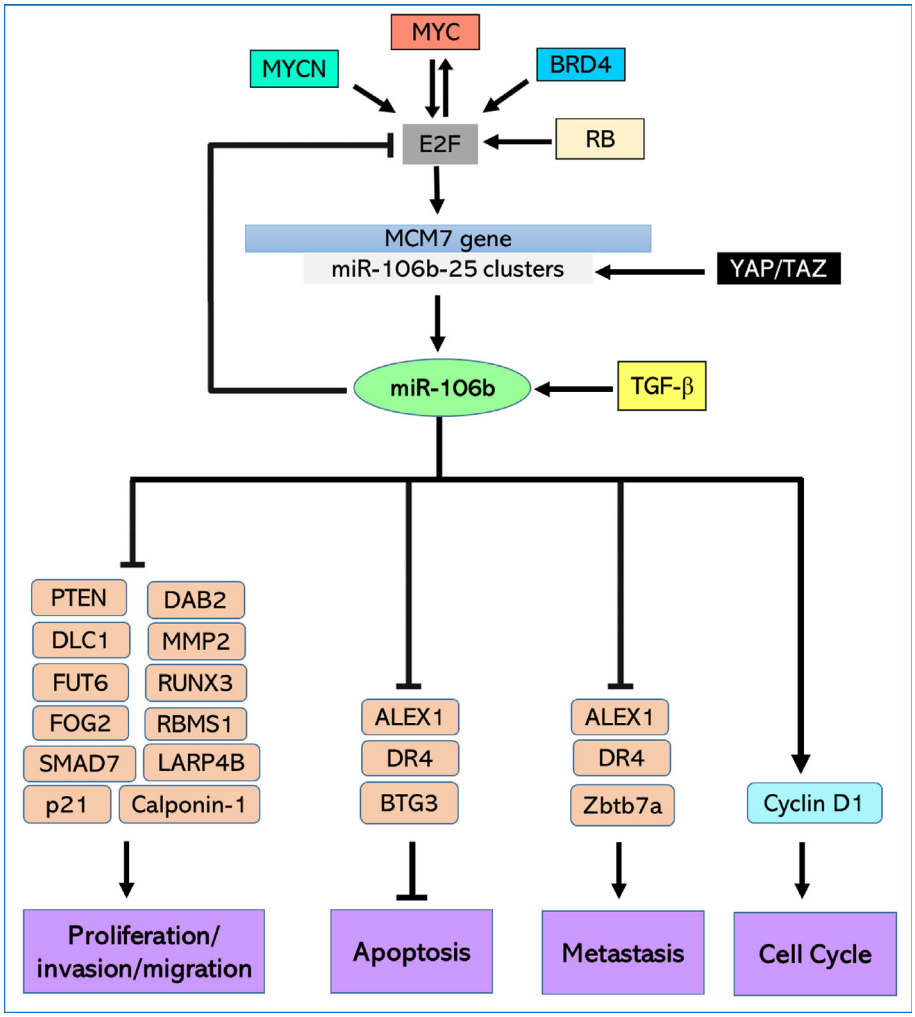

Figure 3 Oncogenic miR-106b regulation and its target. miR-106b-25 cluster is located in the intron region of the *MCM7* gene. miR-106b family is mainly regulated through E2Fs which have several transcriptional sites in MCM7 promotor and directly regulate miR-106b family and in turn control E2F expression. MYC, MYCN, BRD4, and RB upregulate the expression of E2Fs. YAP/TAZ and TGF-β directly regulate the expression of miR-106 family, independent of MCM7. The miR-106b family targets multiple genes involved in different biological functions like proliferation, apoptosis, cell cycle, migration, invasion, and metastases.

regulate several miRNAs including miR- 106b-25 cluster.[49,50] In lung cancer, *YAP/TAZ* acts as an oncogene and regulates miR-106b-25 through *MCM7* gene and its hosted miRs transcription and regulates promote cell proliferation.[49]

Breast cancer

BCa is by far the most common invasive cancer in females and the leading cause of cancer mortality worldwide.[51] An estimated 276,480 new cases and 42,170 new deaths will be reported in the United States (US) in 2020.[52] Breast cancer management employed various approaches like locoregional surgery and radiation therapy and systemic therapy.[53] However, some proportion of patients with early-stage of breast cancer develops recurrence in a few years.[54,55] This explains a need for further improvement in the outcome and the problem of therapeutic resistance in breast cancer patients. Studies have found that miR-106b expression is elevated in breast tumor than non-tumor tissues and associated with breast cancer progression. The author showed that miR-106b regulates several cellular processes in breast cancer *in vitro* and tumor growth *in vivo* and found that high miR-106b lowered the PTEN level in breast cancer and suggested that PTEN is immediate target of miR-106b. In addition, targeting AKT inhibits the ability of proliferation, migration and invasion ability in breast cancer cells. This suggest that miR-106b regulate cell progression through PTEN suppression in breast cancer. Moreover, upregulation of miR-106b promoted tumor growth in xenograft mouse model and *vice versa*. These results conclude that miR-106b promoted breast cancer progression and function as an oncogene.[56]

Another study showed that miR-106b links with poor survival in invasive breast cancer patients. Zheng et al reported that miR-106b level is 2.4-fold higher in BCa tissue as compared to benign tumors and correlated with more advanced disease and bad prognosis in BCa patients. These results demonstrated that miR-106b role in tumor metastasis regulation and might be a prognostic marker for

recurrence in breast cancer.[55] miR-106b seed family member -miR-106-5p is found to be increased in breast cancer cells and activates Rho/ROCK1 pathway by targeting Calponin-1 in breast cancer cells. The author showed that inhibition of miR-106-5p led to a significantly enhanced CNN1 protein level or *vice versa* in breast cancer cells. Overexpression of CNN1 results in decreased cell proliferation, cell migration, and cell adhesion but accelerates the apoptosis rate in breast cancer cells. Forced overexpression of CNN1 led to a decrease in the mRNA and protein level of ROCK1 and protein level of Rho. Targeting the Rho/ROCK1 pathway relieves the effect of CNN1 on BCa cell proliferation and invasion. This suggests that miR-106-5p could lead to breast cancer progression.[29]

In addition, the miR-106b expression is inversely proportional to the Fucosyltransferase 6 (FUT6), fucosyltransferase (FUT) family member leading to advanced cancer stages and poor prognosis in BCa. This study suggests that miR-106b inhibition increased the FUT6 expression and resulted in a decrease in cell proliferation, invasion, and migration.[57] The miR-106b-25 cluster activates the NOTCH1 signaling pathway and decreases E3 ubiquitin ligase expression- NEDD4L resulting in breast cancer initiation.[26] Interestingly, the authors showed that the miR-106b-5p expression could predict the progression and recurrence in BCa *in situ* via the TGF-β pathway.[30]

Prostate cancer

PCa is noncutaneous cancer in men worldwide.[58] An estimated 191,930 new cases and 33,330 new deaths will be reported in the US in 2020.[52] Despite the different therapies, advanced prostate cancer often develops therapeutic resistance to traditional therapies. Thus, a novel approach is needed to improve targeted therapies that target additional pathways in the growth and progression of prostate cancer. miRNAs have gained significant attention to prostate cancer progression.[59,60] For example, miR-106b contributes to tumor viability and migration and acts as an oncogene in PCa. Similar to breast cancer, miR-106b is overexpressed and inversely proportional to PTEN in prostate cancer.[27] In prostate cancer, miR-106b expression is linked with tumor development and disease recurrence by targeting Caspase-7 and focal adhesion.[61] Also, miR-106b has been shown to cause cell cycle arrest when p21 is downregulated in response to radiation therapy in PCa cells. Here, the authors demonstrated that expression of miR-106b increased three-fold after radiation and suppressed radiation-induced p21 activation in LNCaP prostate cancer cells. This study strongly supports that miR-106b directly targets and inhibits p21 and regulates G2/M cell cycle arrest.[62]

Another study demonstrated that miR-106b possesses an anti-apoptotic role in PCa by targeting p21 and E2F1 and leads to inhibition of caspase activity.[63] Yin et al showed that miR-106b is overexpressed in prostate cancer tissue compared to paracancerous tissue. *LARP4B* (La related protein 4B), a LARP family member, is reported as a target gene and act as a tumor suppressor in PCa. LARP4B expression is shown to be lower and inversely proportional to miR-106b in PCa. miR-106b overexpression considerably suppresses the cell viability, invasion, and migration of PCa cells by regulating the Ki67 expression (Proliferation marker), Matrix Metalloproteinase 2 (MMP-2), Cluster of Differentiation 44 (CD44), Smad2 in prostate cancer cells.[64] In addition, Liang et al also reported that miR-106b-25 expression is increased in LNCaP and PC-3 prostate cancer cells in hypoxia conditions and suppresses REST expression (RE-1 Silencing Transcription Factor) in this condition. This suggests the inverse relationship between miR-106b and REST in prostate cancer cells. Moreover, they showed that REST is downregulated and induction of at least one member of the miR-106b−25 cluster in high Gleason score (≥8) Prostate tumor analysis.[65]

In the meta-analysis of human prostate biomarkers, miR-106b overexpression is significantly correlated with poor recurrence-free survival and suggested as a biomarker for diagnosing and predicting prostate cancer.[66,67] Recently, a barely described RNA-binding protein (RBMS1) has been identified as a regulatory target of miR-106b. RBMS1 is shown to interact with miR-106b directly and is inversely proportional to miR-106b expression. Higher expression of miR-106b leads to loss of RBMS1 and influenced the cell growth, colony formation, and gap closing in prostate cancer tissue/cells.[68]

Hepatocellular carcinoma

HCC is one of the aggressive types of liver cancer worldwide. HCC treatment selection depends on various aspects, like tumor characteristics, age, liver dysfunction, severity, and local expertise. Despite the recent advances in therapeutics, cancer-related death is continuing to rise worldwide.[69] Thus, identifying a new treatment approach and understanding the molecular mechanism involved in the HCC progression is needed. Several findings have shown that miR-106b and its member participates in HCC and associated with poor prognosis.[70−72] Yen et al showed that miR-106b expression is increased and linked with tumor progression and poor survival and increases recurrence rates in HBV-associated HCC patients. Moreover, patients with the well-differentiated HCC significantly showed lower expression of miR-106 compare to moderate and poor differentiation HCC patients, suggesting that miR-106b contributes to differentiation and poor survival with high recurrence chance.[72,73]

Interestingly, overexpression of miR-106b upregulates the cell cycle regulator-Cyclin D1 through adenomatous polyposis coli (APC) downregulation to control the entry into the G1/S transitional phase.[74] Smad-7 is also identified as a miR-106b target and regulates the expression of TGF-β1 and p-SMAD3 and results in miR-106b promoting the cell growth, migration, and EMT process through suppression of epithelial cell marker E-cadherin.[75] RhoGTPases are also identified as an indirect target of miR-106b and control stress fiber migration and cell migration.[76] Xu et al proposed that targeting miR-106b helps to overcome the tolerance of TNF-related apoptosis-inducing ligand (TRAIL) in HCC. They reported that miR-106b inhibitors increase Death receptor 4 (DR4) expression by direct targeting and augments TRAIL and therefore lower the acquired resistance to TRAIL.[77] POK transcription factor family 15

member - Zinc finger and BTB domain-containing protein 7A (Zbtb7a) is known to be the target of miR-106b, which plays a key role in tumorigenesis. miR-106b suppresses Zbtb7a translation and inhibits apoptosis.[78]

Seed family member, miR-106-5p expression was found to be increased in HCC and shown to exhibit cancer stem cell properties and regulate cell migration by PTEN via PI3K/AKT pathway. Like other cancer types, miR-106-5p downregulates the PTEN expression in HCC and plays an important role in metastases in HCC cells, indicating the inverse relationship between miR-106b-5p level and PTEN. In addition, patients with a low level of PTEN are linked with more aggressive characteristics and more prolonged survival in patients with high PTEN expression.[33] In another study, HCC clinical showed that the higher expression of miR-106b-5p linked with bad prognosis and advanced TNM stages in patients. Functionally, miR-106b-5p accelerates the proliferation rate and invasion ability in HCC cells, and inhibition of miR-106b-5p by inhibitor lowers the cell proliferation rate and invasion ability. Runt-related transcription factor 3 (RUNX3), tumor suppressor, has been shown to direct miR-106-5p in HCC cells and functionally involved in the TGF- β mediated signaling pathway.[79,80]

miR-106b overexpression enhances the cell viability and cell invasion by RUNX3, and targeting RUNX3 might reverse this phenotype.[81] Yu et al also demonstrated overexpression of miR-106b-5p in HCC tissue associated with the patient's aggressive clinicopathological features. In addition, miR-106-5p overexpression promotes cell proliferation and invasion through FOG2 regulation. Furthermore, overexpression of miR-106b-5p decreases FOG2 (transcriptional regulator friend of Gata 2) expression and enhances cell proliferation and invasion of the HCC cells.[7] miR-106b has been shown to target another tumor suppressor protein, disabled homolog 2 (DAB2). Expression of DAB2 is detected in HCC and plays a role in proliferation and migration. DAB2 is a negatively correlated and miR-106b direct target. Overexpression of miR-106b inhibits DAB2 and promotes the cell proliferation and ability of migration in HCC cells and suggested that miR-106b promote the HCC progression by DAB2 downregulation.[82] Epidemiological studies have shown the role of hepatitis B "e" antigen (HBeAg) in the induction of miR-106b and enhance cell growth by targeting the retinoblastoma gene.[83] Circulating miR-106b in serum identified as a prognostic biomarker for HCC patients[84,85] and in patients treated with Transcatheter arterial chemoembolization.[86]

Lung cancer

Lung Cancer is a malignant tumor and one of the leading reasons for cancer mortality globally. An estimated 228,820 new cases and 135,720 deaths from lung cancer will be reported in the US in 2020.[52] Despite the great improvements in lung cancer therapeutics, the prognosis remains poor. Most patients are diagnosed at stages III or IV before therapy, and the 5-year survival rate is less than 18%. Thus, there is a need to develop a detailed understating of tumor development from different aspects.[87,88] Reports suggest that miR-106b is increased in lung cancer patients and cell lines and enhances invasion and migration in lung cancer cells. Similarly, miR-106b directly regulated PTEN mRNA and protein expression in lung cancer cells and increase cell migration and invasion ability. In addition, they showed that the miR-106b serum exosomal level is positively correlated with TNM stages and lymph node metastasis.[89]

Other studies showed that miR-106b -5p targets BTG anti-proliferation factor 3 (BTG3) in lung cancer cells. miR-106b-5p involves in tumor formation by suppressing the BTG3. Expression of BTG3 is reported to suppress proliferation, the progression of the cell cycle, and metastasis. The authors showed that miR-106b-5p is highly expressed in non-small-cell lung cancer (NSLC) cells, promotes proliferation and caspase-mediated cell death inhibition by negatively regulating BTG3 through direct interaction and binding to BTG3-3′UTR.[90] In addition to regulating cancer initiation and progression, miR-106-5p is involved in the resistance to chemotherapy agents like cisplatin in NSCLC. This study demonstrated that miR-106b-5p directly targets polycystic kidney disease-2 (PKD2) through direct interaction in cisplatin-resistant NSCLC cells. This indicates that miR-106b-5p-mediated regulatory mechanism of cisplatin chemosensitivity NSCLC.[91]

The miR-106b cluster regulates the β-TRCP2 expression by directly targeting the β-TRCP2 transcript, augments cell invasion, and migration potential through Snail upregulation, which is known as β-TRCP2.[92] Transforming Growth Factor-β (TGF-β) Receptor 2 (TGFBR2) shows tumor suppressor activity and is found to be downregulated in cancers, including NSCLC. The oncogenic miR-106b-25 cluster involves in TGFBR2 regulation in NSCLC and post-transcriptionally repress TGFBR2 level.[50]

Gastric cancer

GC is the leading cause of cancer mortality globally with a poor prognosis.[93,94] Treatment for gastric cancer includes surgery, radiation, chemotherapy, and neoadjuvant therapy, which shows improvement, but patients develop advanced stage due to low screening at early diagnosis.[94,95] Due to poor prognosis, development of resistance to conventional therapy, late diagnosis, and search for biomarker remains a major obstacle in gastric cancer.[9,96] Several studies reported that miRNAs dysregulation was found to be involved in gastric cancer progression.[97] The class of miRNAs has been identified as a prospective biomarker in GC early detection.[98] Among these miRNAs, miR-106b significantly upregulated in the gastric cancer[8,99] and genetic association with gastric cancer.[100] In addition, large scale analysis, miR-106b plasma concentration is significantly higher in GC patients as compared to control.[101] Studies have shown that miR-106b alters the feature of cancer stem cell (CSC) by direct regulation of SMAD7 and subsequently inhibits TGF-β in CD44-positive GC cells.[102] Yang et al also demonstrated that miR-106b expression is higher in cancer-associated fibroblasts (CAFs) from GC and linked with poor prognosis, promote cell migration and invasion through PTEN.[103]

Recently, miR-106b role in metastasis of early GC has been reported and found that miR-106b expression is more in the metastasis tissues compared with non-metastasis tissues. In this study, miR-106b directly targets a novel

tumor suppressor gene, *ALEX1*, which is known to suppress gastric cancer metastasis and inhibit apoptosis through the JAK/STAT pathway both *in vitro* and *in vivo*.[104] Studies have shown that miR-106b-25 cluster, especially miR-106b, is upregulated in gastric tumor subsets and correlated with lymph node metastases, distant metastasis, and TNM stage[43,105,106] and regulated by E2F1; in turn, miR-106b and miR-93 downregulates the E2F1 expression through negative feedback loop.[42,43] Furthermore, miR-106b upregulation impairs the TGF-β pathway and regulates CDKN1A and BIM and suggested that the miR-106b-25 cluster is involved in TGF-β resistance development.[43] In addition to TGF-β resistance, miR-106-5p has been reported to be involved in resistance *via* TNF-related apoptosis-inducing ligand (TRAIL), known to promote apoptosis in cancer cells.[107]

Esophageal squamous cell carcinoma

In ESCC, miR-106b works as an oncogene and promotes proliferation, invasion, and metastases. Recently, Zhang et al showed that miR-106b expression enhanced in ESCC tissues. Functionally, they showed that targeting miR-106 with inhibitor significantly decreased wound healing ability as compared to control groups in EC-1 cells. Also, miR-106 inhibition could inhibit the induction of EMT in ESCC cells. Furthermore, they demonstrated that miR-106b directly targets PTEN and involves in invasion, metastases, and proliferation. Downregulation of PTEN in miR-106b treated cells rescued the EMT induction in ESCC cells and suggested that miR-106b mediated EMT depends on PTEN expression.[108] In recent years, increased miR-106b expression is involved in lymph node (LN) metastases and promotes cell invasion and migration through epithelial—mesenchymal transition (EMT) via SMAD-7 downregulation.[109]

Similarly, another study proved that miR-106b is linked with the clinicopathological features of ESCC. This study showed that miR-106b overexpression is associated with smoking, TNM classification, and LN metastasis and smoking. Also, low miR-106b expression in patients showed a higher survival rate compare to patients with increased expression.[110]

Colorectal cancer

CRC is the most lethal cancer and the third leading cause of cancer mortality globally.[111,112] Overall, colorectal associated death rates have dropped over the years due to early detection because this CRC is curable in its early stage, but incidence rates still remain high.[113,114] Surgery followed by chemotherapy is the first line of treatment in Colorectal cancer, but the prognosis is never favorable.[111] Targeted therapy for advanced-stage tumors has shown an increased survival rate,[111] and new drugs have shown less success and develop resistance.[111,114,115] Several studies showed the role of aberrant expression of miRNAs in CRC initiation, progression, and metastases.[113,116] Zhang et al reported that miR-106b is significantly overexpressed in tissues of metastatic CRC and linked with advanced clinical CRC stage and LN metastasis. Metastatic suppressor gene *DLC-1* has been recognized as miR-106b direct target and inversely

Table 1 miR-106b targets and role in cancer types.

Cancer types	Target genes	Biological role	Reference
Breast Cancer	*PTEN*	Tumor growth	56
	Calponin-1	Cell proliferation and invasion	29
	TGF-β	Proliferation	30
	FUT6	Proliferation, invasion, and migration	57
Prostate Cancer	*PTEN*	Cell viability and migration	27
	Caspase-7	Tumor development and disease recurrence	61
	P21, E2F1	Cell cycle arrest, anti-apoptotic	62,63
	LARP4B	Tumor viability and metastases	64
	REST-1	Neuronal markers	65
	RBMS1	Growth, colony formation & gap closing	68
Hepatocellular Carcinoma	*PTEN*	Aggressiveness and disease-free survival	33
	Cyclin-D1	Cell cycle	74
	SMAD7	Cell growth, migration and EMT	75
	Rho/GTPases	Migration	76
	TRAIL	Proliferation, apoptosis, and resistance	77
	Zbtb7a	Apoptosis	78
	RUNX3	Proliferation, invasion, migration and angiogenesis	79—81
	FOG2	Proliferation and invasion	7
	DAB2	Proliferation and migration	82
Lung Cancer	*PTEN*	Migration and invasion	89
	BTG3	Proliferation and anti-apoptosis	90
	PKD2	Resistance to chemotherapy	91
	β-TRCP2	Invasion and migration	92
	TGFBR2	Cell proliferation, apoptosis	50
Gastric Cancer	*E2F1*	Apoptosis, Metastases, TNM stages	42,43
	CDKN1A & BIM	Cell cycle arrest and Apoptosis	43
	SMAD7	Cancer stem cell characteristics	102
	PTEN	Proliferation, invasion	103

(*continued on next page*)

Table 1 (*continued*)

Cancer types	Target genes	Biological role	Reference
		and migration	
	ALEX1	Metastasis, apoptosis	104
	TRAIL	Apoptosis	107
ESCC	*PTEN*	Proliferation, invasion, migration, EMT	108
	SMAD7	Invasion, migration and metastasis	109
CRC	*DLC-1*	Cell migration and invasion	117
	PTEN, *P21*	Cell radioresistance	118

correlated in CRC tissues. Overexpression of miR-106b enhances cell migration and invasion via DLC-1[117]. In addition, miR-106b involved in cell radioresistance via its direct target PTEN and p21 in colorectal cancer in *in vivo* & *in vitro* studies.[118] Recently, a meta-analysis study suggested that the miR-106 family is participating in the CRC initiation, development, and progression and a promising therapeutic biomarker for CRC in meta-analysis.[119]

Conclusions

In recent years, miR-106b and its family members have emerged as putative oncogenes that can target multiple genes and promote tumor progression via different cancer signaling pathways (Table 1). This review discussed the evidence of miR-106b family members' role in cancer and contributed to resistance against anti-cancer therapies. Despite the advances in therapy, cancer cells develop resistance to therapies such as radiation therapy, chemotherapy, and targeted therapies by different mechanisms, including genetics or epigenetic changes in the cancer cell. Recently, miRNAs have become known as a prospective biomarker in different cancer types and their therapeutic potential. Expression of miRNAs has shown to increase in different cancer types and involve in cancer progression. In the current era of conventional therapy, miRNA-based therapies show a novel approach in cancer management. miRNA-based therapy like miRNA mimics and antagomir has been developed to modulate the tumor microenvironment and inhibits tumor progression.

Moreover, miRNA-based therapies have progressed in clinical trials and will provide more understanding of this new cancer therapeutic approach. There are some challenges in this approach, like 1) effectiveness of miRNA-based therapy depends on the precise, efficient and suitable delivery of miRNA and 2) comprehensive understanding of the biological roles of circulating miRNAs are a potential barrier. Despite all the challenges, the miRNA targeted approach holds strong potential in cancer therapeutics. The conventional therapies are partially effective and/or develop resistance later; combinatorial approaches with miRNA-based therapy could open new cancer therapeutics strategies. miR-106b and other family members could be attractive and potential biomarkers in different cancer types for detection, diagnosis, and prognosis assessment in the tumor. In summary, targeting miR-106 with novel approaches could become potential strategies in patients who develop resistance to conventional therapies to overcome the resistance and bring new hope to cancer patients.

Conflict of interests

The author declares no conflict of interest.

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