World Journal of Gastroenterology

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DOI: 10.3748/wjg.v22.i5.1787

World J Gastroenterol 2016 February 7; 22(5): 1787-1799
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

MicroRNA aberrations: An emerging field for gallbladder cancer management

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Conflict-of-interest statement: No potential conflicts of interest.

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Received: October 6, 2015
Peer-review started: October 8, 2015
First decision: November 5, 2015
Revised: November 12, 2015
Accepted: December 21, 2015
Article in press: December 21, 2015
Published online: February 7, 2016

Abstract

Gallbladder cancer (GBC) is infrequent but most lethal biliary tract malignancy characterized by an advanced stage diagnosis and poor survival rates attributed to absence of specific symptoms and effective treatment options. These necessitate development of early prognostic/predictive markers and novel therapeutic interventions. MicroRNAs (miRNAs) are small, non-coding RNA molecules that play a key role in tumor biology by functioning like tumor suppressor- or oncogenes and their aberrant expression are associated with the pathogenesis of several neoplasms with overwhelming clinical implications. Since miRNA signature is tissue specific, here, we focused on current data concerning the miRNAs abberations in GBC pathogenesis. In GBC, miRNAs with tumor suppressor activity (miR-135-5p, miR-335, miR-34a, miR-26a, miR-146b-5p, Mir-218-5p, miR-1, miR-145, mir-130a) were found downregulated, while those with oncogenic property (miR-20a, miR-182, mir-155) were upregulated. The expression profile of miRNAs was significantly associated with GBC prognosis and prediction, and forced over-expression/ inhibition of these miRNAs was shown to affect tumor growth and development. Further, differential expression of miRNAs in the blood samples of GBC patients suggest miRNAs as promising noninvasive biomarker. Thus, miRNAs represent potential candidate for GBC management, though many hurdles need to be overcome before miRNAs therapy can be clinically applied to GBC prevention and treatment.

Key words: Gallbladder cancer; MicroRNA; Aberrations; Tumor suppressor gene; Oncogene; Biomarker; Therapy

Core tip: Emerging evidences have shown a clear link between microRNAs (miRNAs) expression profile

and carcinogenesis. In addition, miRNA has been shown a promising biomarker with devastating clinical implications in various cancer. Recently, several studies have investigated miRNA signature or dysregulation in gallbladder cancer (GBC) pathogenesis. In this review, we aimed to amalgamate the available data to predict the clinical significance of miRNA aberration in GBC. Our findings suggested miRNAs as a promising biomarker and therapeutic tool for GBC management, however, there is a long way to go.

Chandra V, Kim JJ, Mittal B, Rai R. MicroRNA aberrations: An emerging field for gallbladder cancer management. *World J Gastroenterol* 2016; 22(5): 1787-1799 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i5/1787.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i5.1787

INTRODUCTION

Although it is rare, gallbladder cancer (GBC) is a highly aggressive and fatal disease with wide geographical, ethnic, and gender specific variations in its incidence[1,2]. Since there are no specific signs, symptoms or reliable sensitive markers, GBC is usually diagnosed at advance stages and the outcome is dismal[3,4]. Neither radiation nor conventional chemotherapy have been shown to significantly improve survival or quality of life for GBC patients. The 5-year survival rate is 32% in patients with lesions confined to the gallbladder mucosa, while there is only a 10% one year survival rate for patients with more advanced lesions[5]. Early diagnosis can have a significant curative impact with surgery as the only therapeutic option[6]. However, our knowledge regarding the molecular pathobiology of GBC is rather limited owing to the scarcity of published studies. Thus, exhaustive efforts are needed to identify authentic tumor markers that will facilitate early detection of GBC and add to better therapeutic options.

MicroRNAs (miRNAs) are short (18-25 nucleotides in length) noncoding RNAs that function as master regulators of gene expression regulating nearly 60% of human genes[7,8]. To date, more than 10000 miRNAs have been identified, and shown to regulate various biological processes and numerous developmental and physiological processes[9-11]. Further, mis-expressed miRNAs have also been associated with several pathological conditions[12,13].

MiRNAs are now well established to promote cancer progression by functioning as either tumor suppressors or oncogenes collectively known as "oncomirs"[14]. Oncogenic miRNAs act directly on transcripts with pro-apoptotic or anti-proliferative roles[15]. Conversely, tumor-suppressor miRNAs repress the expression of oncogenes and/or genes that control cell differentiation or apoptosis[16]. Numerous studies have looked for the association of miRNA aberrantions with cancer progression and its prognostic implications[17-19] suggesting circulating and tissue miRNA profiles as superior diagnostic and prognostic biomarkers and therapeutic targets for cancer[20-22]. In addition, tumour-based miRNA signatures were suggested to identify tissue of origin of cancer[23,24]. However, information regarding the role of miRNAs in GBC and systematic evaluations of miRNA panels in GBC is limited. Therefore, in the present review, we aimed to describe the role of miRNA deregulation in tumorigenesis, specifically in GBC to unravel its role in GBC pathophysiology and potential for use in early detection and prognosis.

MIRNA, ITS BIOGENESIS AND DYSREGULATION

MiRNAs are endogenous RNA molecules that are ubiquitous in animals, plants, and viruses but, expressed in a tissue-specific manner[25]. These functions mainly as negative regulators of post-transcriptional gene expression by binding to the 3' untranslated region (UTR) of target mRNAs, thereby either transcriptionally destabilizing/degrading or transnationally inhibiting them (or both) depending on the degree of miRNA-mRNA complementarity[26,27]. Since miRNAs bind to target mRNAs through imperfect pairing, a single miRNA often regulates the expression of multiple genes[28]. Moreover, one gene can be targeted by multiple miRNAs[29].

MiRNA biogenesis involves three main steps, transcription, nuclear processing, and nuclear export to the cytoplasm (Figure 1). In the nucleus, RNA polymerase Ⅱ transcribes a precursor of miRNA (pri-miRNAs) having a stable stem-loop[30] which is cleaved by microprocessor complex (Drosha and Pasha) releasing a hairpin-structured pre-miRNA (60-100nt)[31,32]. Pre-miRNA is exported to the cytoplasm by exportin-5 (XPO5) and subsequently cleaved by Dicer-TRBP (TAR RNA-binding protein)-PACT (or PRKRA) complex producing 20-24 nt miRNA duplexes. These miRNA duplexes, known as miRNA: miRNA*, become associated with argonaute (Ago) proteins, which are central to RNA-induced silencing complex (RISC) function[33,34]. Next, RISC is released and degrades one strand (passenger strand) from miRNA:miRNA* duplex, while another remains associated with RISC in a complex known as mature miRNA (or guide strand miRNA), which interacts and regulate the target genes[35].

The mechanism of miRNA regulation is finely controlled by various nuclear and cytoplasmic factors under three main steps, transcription, biogenesis and binding at target sites. Transcription of miRNA is under the control of various transcription regulators (p53, E2F, or cMyc) with oncogenic or tumor suppressor

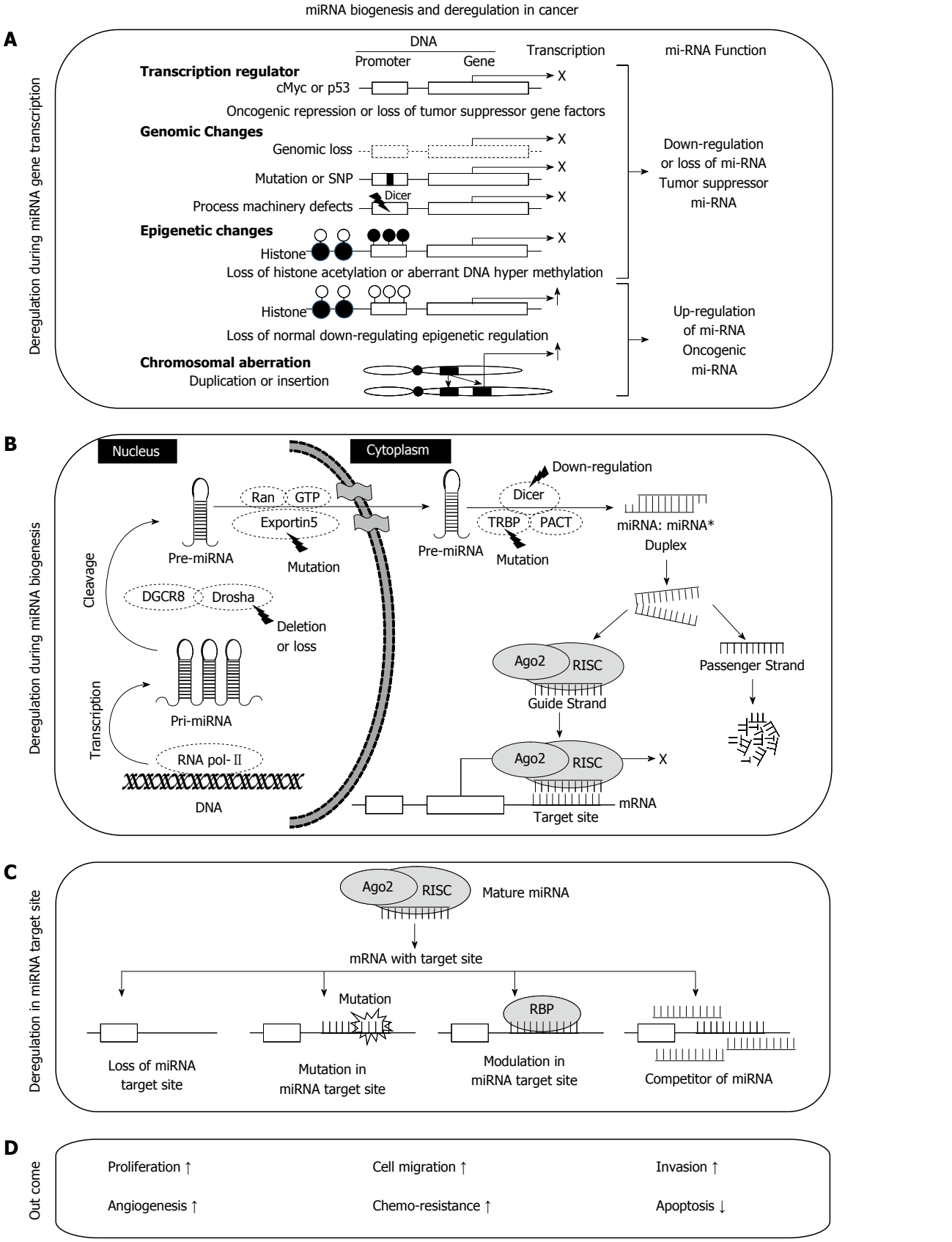

Figure 1 Systematic representation of microRNA biogenesis, deregulation and function. A: MicroRNA (miRNA) deregulation at the transcription level includes transcription regulation, genomic changes, epigenetic changes (such as CpG island methylation, histone methylation or acetylation at the promoter regions) and chromosomal aberrations such as duplication or insertions; B: Canonical pathway of miRNA biogenesis with common deregulation in cancer; C: Deregulation of miRNA target sites and mechanisms preventing miRNA interaction with its target sites such as loss of target site, mutation or SNP, modulation, competition or pseudotargets in the target site; D: Outcome of deregulated miRNA functional mechanism.

functions. Epigenetic modifications at the promoter regions of specific miRNA coding genes and genomic changes including chromosomal rearrangements and mutation or SNP may also lead to miRNA aberrations. Biogenesis and maturation of miRNA occurs under the control of various enzymes or co-regulators such as exportin 5, Drosha, Dicer, TRBP, Ago2 and RISC. However, they are frequently deregulated under various pathological conditions. For example partial deletion of Drosha and/or Dicer1[36,37] and mutation in TRBP or Exportin[38,39] leads to aberrant expression of miRNAs in different cancers[36,40,41].

MIRNAS AND CARCINOGENESIS

MiRNA deregulation has been well established in most cancer types[42,43]. Various studies have suggested that miRNA expression is commonly down-regulated in human tumors, while some studies also reported miRNA over-expression in cancer[44]. In general, miRNAs are involved in transcriptional regulation of important genes that control key signaling pathways involved in tumorigenesis and tumor development such as apoptosis, cellular proliferation, angiogenesis and regulation of the microenvironment. Here, we discuss the roles of miRNAs in regulation of common steps in carcinogenesis.

MIRNA AND CELL CYCLE REGULATION

MiRNAs control cell cycle directly by targeting cell cycle regulatory genes and indirectly by targeting various signaling pathways[45-48]. Cyclins (cyclin A, B, D, E) and cyclin dependent kinases (CDK 2, 4, 6) promote the cell cycle with subsequent inactivation of Rb protein and activation of E2F transcription factor[49-51]. Conversely, the INK4 (p16, p15, p18 and p19) and Cip/Kip (p21, p27, and p57) families suppress the cell cycle by activating CDK inhibitor[52-55]. These entire genes are well known targets of miRNAs (Supplementary Table 1).

Tumor suppressive miRNAs inhibit the cell cycle through repression of a wide spectrum of positive regulators[56,57]; however, oncogenic miRNAs such as miR-17-92, promote cell cycle progression by targeting its negative regulators[58]. Upregulation of miR-221/222 and miR-21 has been shown to promote G1/S transition[59], while over-expression of miR-16 and mir-34 family miRNAs may lead to G0/G1 arrest[60]. Further, alteration of miRNA levels is associated with cell cycle dysregulation contributing to carcinogenesis[61]. The let-7 and miR-15 families which are major tumor-suppressor miRNAs are frequently lost or downregulated in various cancers[46,62]. Additionally, the mir-17-92 and mir-221/222 are often upregulated in cancer inducing cell proliferation through activation of the cell cycle and Akt pathway[63,64]. Further, recent studies have demonstrated a complex interaction between miRNAs and several transcription factors (p53, cMYC) governing the cell-cycle[65,66].

MIRNA AND APOPTOSIS

Diminished apoptosis is considered a hallmark of cancer progression[67]. Apoptosis may occur *via* either an intrinsic or extrinsic pathway. miRNAs dysregulation has been shown to control both the extrinsic and intrinsic apoptotic pathway, especially in cancer cells, by controlling the expression of pro-apoptotic and anti-apoptotic protein (Supplementary Table 2). In general, pro-apoptotic miRNAs (mir-15, mir-16, let-7f, mir-34, mir-1, mir-101, mir-29) target anti-apoptotic genes or negative regulators of apoptosis while anti-apoptotic miRNAs (mir-21, mir-133, mir-17-92, mir-206, mir-143, mir-145, mir-155, mir-221/222) target pro-apoptotic genes or positive regulators[68-70]. In cancer cells, the expression of pro-apoptotic miRNAs were demonstrated to decrease, while several anti-apoptotic miRNAs were frequently up-regulated, thereby inhibiting apoptosis[63,71].

P53, an important player of apoptosis, is negatively regulated by mir-125b and mir-380-5p while miR-29 family members were identified as positive regulators by targeting upstream CDC42 and p85α[72]. Further, miR-24 modulates XIAP expression level, while mir-203 and mir-218 regulate survivin expression and consequently regulate the apoptosis threshold in cancer cells[73-75]. In addition, mir-10a, let-7a, mir-144, mir-133, mir-24a and mir-155 were shown to affect caspases activation resulting diminished apoptosis[70,76].

MIRNA IN INVASION, EMT AND METASTASIS

MiRNAs, collectively termed as "metastamir", play significant roles in metastasis by regulating the expression of different genes involved in various steps of metastasis such as EMT, cancer cell detachment, invasion and migration (Supplementary Table 3)[77-80]. mir-200f and mir-203 are well-known epithelial markers that are associated with suppression of EMT and metastasis when over-expressed by targeting ZEB1/2 and Snail1/2 expression[81,82]. mir-221/222, mir-103/107, mir-27, mir-9, mir-155, mir-81a and mir216a/217 are EMT inducer while, mir-30a, mir-34a/b/c, mir-124, mir-203, mir-145, mir-204/211, mir-138, mir-215, mir-708 and mir-205 are EMT inhibitors[83]. Further, miR-143, miR-29b, miR-206, mir-340, miR-218, mir-491-5p, miR-338-3p, let-7, miR-31, mir-21, mir-181 and mir-22/222 regulate extracellular matrix remodeling through modulation of matrix metallo-proteinases in cancer[84].

MiR-10b, mir-21, mir-520c and mir-373 were reported as pro-metastatic miRNAs[85] while let-7, mir-126, mir-335, mir-206 and mir-31 were found to be anti-metastatic miRNAs[86]. Down-regulation of the miR-200f, miR-148a miR-148b and miR-9 family, and

upregulation miR-210 is believed to be a metastasis-specific feature[78].

MIRNA AND ANGIOGENESIS

Angiogenesis is mediated by cross-talk between pro and anti-angiogenic signaling pathways[87]. Downregulation/depletion of the Dicer and Drosha were shown to impair angiogenesis demonstrating the importance of miRNA in angiogenesis[88]. Several angiomirs targeting angiogenesis have been also identified (Supplementary Table 4)[89]. Specifically, miR-17-92 cluster, miR-27b, miR-126, miR-130a, miR-210, miR-296, mir-21, mir-31, let-7f and mir-378 have pro-angiogenic function and promote tumor angiogenesis, while miR-221 /miR-222, miR-320, mir-26a, miR-15, miR-16, miR-20a and miR-20b are anti-angiomiRs[90-93].

MiRNAs have been also shown to regulate endothelial cell (EC) function, vascular development, physiology and disease[90,94-97]. ECs demonstrated high expression of miR-21, let-7f, miRNA-23-24 cluster, mir-15b, mir-16, mir-100, miR-126, miR-221/222 and miR-17-92 cluster[92,98]. miR-126 was suggested to be an EC specific miRNA that promotes angiogenesis response to VEGF and bFGF[99].

MIRNA AND CANCER METABOLISM

Metabolic reprogramming constitutes the unique biochemical characteristic and the very origin of cancer[100]. Recently, miRNAs were established to serve as master supervisors of energy metabolism such as carbohydrate, lipid, insulin, protein and nucleic acid metabolism, directly by influencing the metabolic machinery (transporters), or indirectly by modulating the expression of metabolic enzymes/kinases or production of certain metabolites *via* targeting the genes encoding them (Supplementary Table 5)[101-103]. The miRNA regulation of carbohydrate metabolism involving glucose transporters (GLUTs) and the key enzymes (HKs, GAPDH, PFK1 *etc.*) has been extensively investigated[104-106]. miRNAs dregulations has also been found to affect key molecules associated with various signaling pathways leading defective metabolism in cancer such as p53, HIF-1alpha, Ras, AKT, AMPK and cMyc[107-109].

MIRNA ABBERATIONS AND GBC

Emerging evidence has shown a clear link between miRNA alterations and tumor progression from normal phenotype[110-113]. Although, miRNA profile has been implicated as a potential biomarker and therapeutic target for cancer[114-118], the characterization of miRNA alterations in GBC, its relationship with GBC pathogenesis, and prognosis has been only poorly deciphered based on a limited number of studies, to date (Table 1)[119].

Aberrations of miRNA processing enzyme in GBC

Initially, Shu *et al*[120] (2012), used immunohistochemistry to investigated the expression of Dicer and Drosha in GBC patients and non-dysplastic gallbladder epithelia. They reported significant downregulation of Dicer or Drosha in GBC than in non-dysplastic gallbladder epithelia, and that the loss of Dicer and Drosha expression was closely related to the metastasis, invasion, decreased overall survival and poor-prognosis of GBC patients. Since Dicer and Drosha are two key enzymes involved in miRNA production, the loss of expression of these two enzymes is considered to partially account for the down regulation of miRNA expression followed by overexpression of oncogenes or survival and proliferation associated genes in GBC. Thus, they provided the first evidence of a role of miRNA in GBC pathogenesis.

MiRNA aberrations in animal models of GBC

Kitamura *et al*[121] (2012) compared the expression of miRNA in GBC from BK5.erbB2 mice (animal model for GBC) to that in control gallbladders from wild-type mice using a microarray. They reported significant up-regulation of miR-106a, miR-96, miR-223, miR-27a miR-17, miR-15b, miR-142-5p, miR-142-3p and miR-21 as well as down-regulation of miR-665, miR-714, miR-763, miR-466f-3p, miR-145, miR-193, miR-467e, miR-143, miR-881, miR-720, miR-706, miR-122 and miR-378 in BK5.erbB2 mice compared to normal gallbladder. Furthermore, BK5.erbB2 mice treated with histone deacetylase inhibitor PCI-24781 showed significant downregulation of miR-21, miR-142-3p, miR-142-5p and miR-223 and upregulation of miR-122.

MiRNA aberrations in human GBC tissue samples and cell lines

MiRNAs over-expression in GBC - Oncogenic miRNAs: Mir-155, mir-20a and mir-182 have been reported as oncomiRNAs that promote progression of gallbladder carcinoma when overexpressed (Figure 2).

MiR-155 has been reported to be up-regulated in GBCs as compared with gallbladders with pancreaticobiliary maljunction (P = 0.007) and normal gallbladders (P = 0.04). The higher expression of miR-155 was found to be significantly correlated with aggressive behavior of GBCs such as the presence of lymph nodes, metastasis and vessel invasion, indicating a poor prognosis. Further, GBC cell lines transfected with miR-155 inhibitors showed significant decrease in cell proliferation and invasion. Conversely, cells transfected with miR-155 showed significant increase in cell proliferation relative to negative controls, confirming the role of miR-155 as a potent regulator of proliferation and invasion in GBC. These findings suggest that modulation of the miR-155 level may be applied to the treatment of GBCs, particularly for inhibition of cancer progression such as lymph node invasion. Thus, mir-155 may represent a prognostic

Table 1 MicroRNA de-regulation in gallbladder cancer

Ref.	Source	miRNA	Level	Target gene	Functional characterization	Clinical association with	Function
Kitamura *et al*[121], 2012	GBCs from BK5. erbb2 mice *vs*	mir-106a, mir-96 mir-223 mir-27a mir-17 mir-15b mir-142-5p mir-142-3p mir-21	↑	-	-	-	-
	GBC from wild-type mice	mir-665 mir-714 mir-763 mir-466f-3p mir-145 mir-193 mir-467e mir-143 mir-881 mir-720 mir-706 -mir-122 mir-378	↓	-	-	-	-
Li *et al*[133], 2015	Paired GBC, normal tissue and blood samples	mir-21, mir-370, mir-187, mir-122, mir-202	↑	-	-	mir-187, mir-143, mir-202 were associated with metastasis, TNM	-
		let-7a, mir-200b, mir-143, mir-31, mir-335, mir-551	↓				
Peng *et al*[125], 2013	Paired GBC, normal tissue	mir-335	↓	-	-	Histologic grade, stage, metastasis, poor survival	-
Zhou *et al*[127], 2014	Paired GBC, paracancerous tissue	mir-106a, mir-96 mir-223 mir-27a mir-17 mir-15b mir-142-5p mir-142-3p mir-21	↑	-	-	-	-
		mir-665 mir-714 mir-763 mir-466f-3p mir-145 mir-193 mir-467e mir-143 mir-881 mir-720 mir-706 -mir-122 mir-378	↓	-	-	-	-
		hsa-mir-135a-5p	↓	VLDLR	Cell proliferation, cell cycle distribution	Histologic grade	TSG
Jin *et al*[126], 2014	Paired GBC tissue, tissue	mir-34a	↓	PNUTS	Cell proliferation	Poor prognosis	TSG
Zhou *et al*[128], 2014	Paired GBC, paracancerous tissue	mir-26a	↓	HMGA2	Cell proliferation	Histological grade	TSG
Letelier *et al*[129], 2014	Normal GB, GBC tissue	mir-133a/b, mir-143-3p/5p, mir-991-5p, mir-125b-5p, mir-29c-3p, mir-195-5p, mir-139-5p, mir-29c-5p, mir-100-5p, mir-148a-3p, mir-376c, mir-187-3p, mir-365a-3p, mir-29b-3p, mir-497-5p, mir-654-3p, mir-411-5p, mir-125a-5p, mir-26a-5p, mir-101-3p, mir-495, mir-381-3p, mir-154-5p, mir-99a-3p, mir-328, mir-299-5p, mir-30e-3p, mir-29b-2-5p, mir-379-5p, mir-140-5p, mir-24-1-5p, mir-101-5p	↓	Distinguish GBC from normal samples		-	-
		mir-145-3p/5p	↓	-	Cell growth, cell viability, apoptosis	-	TSG
		mir-1	↓	VEGF-A , AXL	Cell growth, cell viability, apoptosis	-	TSG
Ma *et al*[131], 2014	Paired GBC, normal tissue	mir-130a	↓	-	Cell proliferation, invasion	-	TSG
Cai *et al*[130], 2015	Paired GBC, normal tissue	mir-146b-5p	↓	EGFR	Apoptosis, G1 phase arrest	Carcinoma size, progression	TSG
Ma *et al*[132], 2015	Paired GBC, normal tissue	mir-218-5p	↓	BMI-1	Cell proliferation, invasion	-	TSG
Chang *et al*[123], 2013	Paired GBC, normal GB tissue	mir-20a	↑	SMAD-7	EMT, metastasis	Worse overall survival	OG
Kono *et al*[122], 2014	Paired GBC, normal GB tissue	mir-155	↑	-	Cell proliferation, invasion	Lymph node metastasis, invasion, poor prognosis	OG
Qiu *et al*[124], 2014	GBC, normal tissue	mir-182	↑	CADM1	Cell migration, invasion	Metastasis	OG

GBC: Gallbladder cancer; VLDR: Very-low-density-lipoprotein receptor; PNUTS: Phosphatase 1 nuclear targeting subunit; HMGA2: High-mobility group AT-hook 2; VEGF-A: Vascular endothelial growth factor A; AXL: AXL receptor tyrosine kinase; EGFR: Epidermal growth factor receptor; BMI-1: Polycomb ring finger; SMAD-7: Mothers against DPP homolog 7; CADM1: Cell adhesion molecule 1.

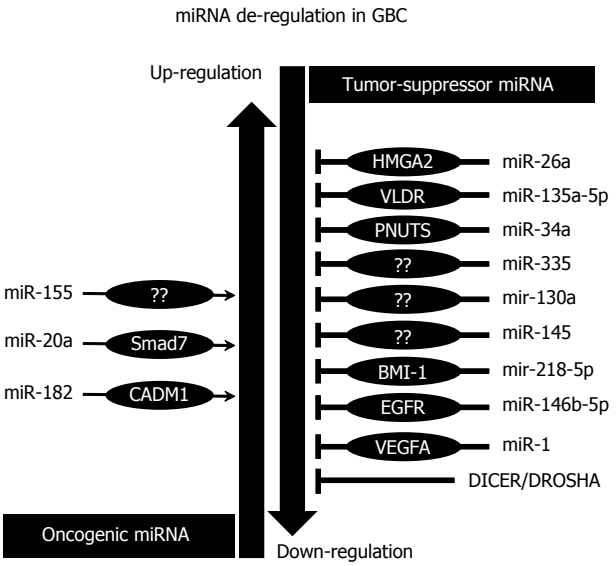

Figure 2 MicroRNA aberrations in gallbladder cancer and their role.

marker and therapeutic target for GBC[122].

Chang *et al*[123] (2013) identified 17 prominent metastatic inducers of GBCs. Among them, mir-20a was found to be highly expressed in tumor tissues as compared to normal gallbladder and was closely associated with local invasion, distant metastasis, and poor prognosis of GBC patients. Patients with higher miR-20a expression exhibited a worse overall survival than those with lower expression. The ectopic expression of miR-20a was shown to induce EMT and enhance metastasis of GBC cells *in vitro* and *in vivo* by directly targeting the 3′ UTR of Smad7 and subsequently promoting nuclear translocation of β-catenin, suggesting that the TGF-β1/miR-20a/SMAD7 axis plays an important role in the progression of GBC.

Another study reported significant upregulation of mir-182 in GBC relative to normal control and in the metastatic tumor when compared with primary tumor that did not metastasize. Upregulation of miR-182 expression in GBC cells was found to promote cell migration and invasion while downregulation of miR-182 inhibited TGF-β-induced cell migration and invasion. They also identified CADM1 as a new target gene of miR-182 that is negatively regulated by mir-182 *in vitro* and *in vivo*. Importantly, re-expression of CADM1 in GBC cells partially abrogates mir-182-induced cell invasion[124].

MiRNAs downregulation in GBC - Tumor suppressive miRNAs: Tumor suppressive miRNAs in GBC include mir-34a, miR-335, miR-135-5p, miR-26a, miR-1, miR-145 and mir-146b-5p which were frequently found to be down-regulated in GBC (Figure 2).

Peng *et al*[125] (2013) demonstrated downregulation of miR-335 in the majority of GBC patients that is associated with aggressive tumor behaviors such as high histologic grade, advanced pathologic T stage, clinical stage, lymph node metastasis and shorter overall survival. Reduced miR-335 expression represents an independent predictor of poor prognosis for overall survival in GBC patients. Later, Jin *et al*[126] (2014) identified mir-34a as a tumor suppressor in GBC. Moreover, they demonstrated significantly lower miR-34a expression in GBC as compared to peritumoral tissue, which correlated with poor prognosis of GBC patients. Forced overexpression of miR-34a reduced the colony-forming ability of $CD44^+CD133^+$ GBC tumor stem-like cells *in vitro* and inhibited tumor growth in a xenograft animal model. This inhibitory effect was associated with downregulation of phosphatase 1 nuclear targeting subunit (PNUTS) expression and a decrease in telomerase length.

By using the miRNA expression profiling chip in four paired GBC and paracancerous tissues, Zhou *et al*[127], 2014 identified aberrant expression of 23 miRNAs in GBC tissue as compared with their paired noncancerous tissue. Among them, miR-135a-5p and miR-26a were considered to significantly influence GBC cell proliferation. miR-135-5p expression was correlated with the neoplasm histologic grade. Ectopic mir-135a expression inhibited GBC cell proliferation *in vitro* and *in vivo* and disrupted cell cycle distribution leading to arrest the cells in the G 1/S phase. miR-135a exerted this function by directly targeting very low density lipoprotein receptor (VLDLR), leading to activation of the p38 MAPK pathway. In a subsequent study, they reported miR-26a downregulation in GBC associated with neoplasm histological grade. miR-26a significantly inhibited the proliferation of GBC cells by targeting high mobility group AT-hook 2 (HMGA2) *via* G1 arrest. Furthermore, they demonstrated that HMGA2 mRNA levels and miR-26a levels were negatively correlated and reintroduction of HMGA2 antagonized inhibition of the GBC cell proliferation by miR-26a[128].

A comprehensive miRNA profiling study showed consistent downregulation of 36 miRNAs separating the GBC and normal samples. Among them, expression of hsa-miR-133a, hsa-miR-133b, hsa-miR-143, hsa-miR-145, hsa-miR-1, and hsa-miR-29c were further validated by qRT-PCR. These miRNAs collectively targeted a number of genes including TGF-β, ErbB3, WNT, MAPK and VEGF, Notch as well as those participating in various biological processes associated with human cancer such as transcription regulation, signal transduction, positive regulation of cell proliferation, cell adhesion and angiogenesis. miR-1 and miR-145 expression were significantly decreased in GBC cell lines. Ectopic expression of miR-1 and miR-145 was shown to decrease cell viability, inhibit colony formation or clonogenic survival and increase apoptosis. mir-1 may act *via* reduced gene expression of VEGF-A and AXL, resulting in inhibition of gallbladder cancer cell growth, *in vitro*[129].

Decreased expression of mir-146b-5p was also reported in GBC tissue, which is significantly correlated

with carcinoma size and development[130]. miR-146b-5p overexpression was found to inhibit cell growth through enhanced apoptosis and G1 phase arrest. Enforced expression of epidermal growth factor receptor (EGFR) reversed the ability of miR-146b-5p to inhibit proliferation suggesting that EGFR is a mediator of the biological effects of miR-146b-5p in GBC[130].

OTHER MIRNAS

HOTAIR's, which are long non-coding RNAs with oncogenic activity, have been found to negatively regulate miRNA-130a expression in GBC, promoting the invasiveness and proliferation of cancer cells. miRNA-130a has tumor-suppressive activity, and has been previously reported to be downregulated in a variety of carcinomas[131]. Later, Ma *et al*[132] (2015) demonstrated that downregulation of miR-218-5p in GBC occurred *via* Colon Cancer-Associated Transcript-1 (CCAT1). Specifically, CCAT1 was found to promote the proliferation and invasiveness of GBC cells by upregulating the miRNA-218-5p target gene, Bmi1, by competitively "spongeing" miRNA-218-5p. Recently, Li *et al*[133] (2015) demonstrated deregulation of 11 miRNAs (upregulated- miR-21, miR-370, miR-187, miR-122, miR-202; and down-regulated- let-7a, miR-200b, miR-143, miR-31, miR-335, and miR-551) in GBC tissue samples relative to neighboring noncancerous tissue.

MiRNA aberrations in blood samples of GBC patients

Li *et al*[133] (2015) demonstrated upregulation of miR-21, miR-200b, miR-187, miR-122, and miR-202 while down-regulation of let-7a, miR-370, miR-143, miR-31, miR-335, and miR-551 in blood samples of GBC patients relative to control blood samples. However, only the level of let-7a, miR-21, miR-187, miR-143, miR-202, and miR-335 was reported to differ significantly between GBC patients and the control. Furthermore, only miR-187, miR-143, and miR-122 were associated with lymphatic metastasis, suggesting that these three miRNAs can be used for GBC prognosis and therapeutic efficacy.

MiRNA genetic variants in GBC

Envisioning the important role of miRNA in carcinogenesis, as well as the role of genetic variants to modulate the miRNA processing and expression, thereby resulting in diverse functional consequences, Srivastava *et al*[134], investigated the association of common potentially functional polymorphisms in pre-miRNA (hsa-miR-146a, hsa-mir-196a2 and hsa-mir-499) with GBC susceptibility in a North Indian population. However, they found no association suggesting that these miRNA variants may not contribute to GBC susceptibility. Recently, we evaluated the association of genetic variants of miR-27a (rs895819), miR-570 (rs4143815) and miR-181a (rs12537), which alter miRNA processing and expression, with genetic susceptibility, treatment response and toxicity (personal communication). None of the studied SNPs were found to be associated with overall GBC susceptibility, survival outcomes of GBC patients (locally advanced, metastatic) and response to chemo-radiotherapy. However, in Generalized Multifactor Dimensionality Reduction(GMDR) analysis, miR-27a$_{rs895819}$, miR-570$_{rs4143815}$, and miR-181a$_{rs12537}$ combination was found to be associated with GBC susceptibility and treatment response while miR-27a$_{rs895819}$-miR-181a$_{rs12537}$ combination was associated with neutropenia toxicity in patients undergoing chemo-radiotherapy suggesting the the cumulatively influence of miRNA variants on GBC susceptibility and treatment outcomes[135].

FUTURE PROSPECTIVE: MIRNA AS A THERAPEUTIC OPTIONS FOR GBC

Currently, the use of miRNA as a viable therapeutic target is the most fascinating area of cancer research that has gain overwhelming amount of importance because (1) miRNA are small molecule comprising of a known and evolutionary conserved sequences; (2) it can target multiple genes and regulate wide range of biological process; (3) the potential targets of a particular miRNAs can be predicted by using various bioinformatical tools; such as miRanda (http://www.microRNA.org), microCosm (previously known as miRBase targets, http://www.mirbase.org), Targetscan (http://www.targetscan.org), or PicTar (http://pictar.mdc-berlin.de); (4) miRNA expression is frequently dysregulated in various cancer; and (5) the cancer phenotype can be changed by targeting miRNA expression[17,136-138]. Consequently, growing evidences have confirmed that restoration of miRNAs signature *i.e.*, inhibition of over-expressed and oncogenic miRNAs by using chemically modified anti-miR oligonucleotides as well as restoration of down-regulated or tumor suppressive miRNAs by using synthetic miRNA mimics or viral expression constructs, constitute a novel treatment strategy for cancer. In addition several miRNAs modulation has been found to reverse the drug resistance in various cancer enhancing the therapeutic implication of miRNAs[139-141].

Till date, several studies have successfully investigated the therapeutic effects of miRNA in preclinical models and xenografts, *e.g.*, reconstitution of miR-34 and let-7 was found to reduce the tumour growth in a murine model of non-small cell lung cancer (NSCLC). On the other hand, depletion of miR-21 in combination therap has been shown to control pancreatic ductal adenocarcinoma in a mouse model. MRX34 (mir-34 mimic) is the first microRNA mimic to enter clinical development for cancer and is currently under phase I clinical trial (NCT01829971) involving primary hepatocellular carcinoma (HCC metastatic liver cancer) patients. Since, mir-34 and let-7 was shown to function

like TSG while mir-21 was found to be oncogenic in GBC, similar miRNA therapy could be also applied for GBC like other cancers. Thus, miRNA holds promising perspectives for GBC management where treatment options are already limited, however, there is still limited study exploring the role of miRNA in GBC and we still need to identify key miRNAs having therapeutic importance in GBC. Moreover, though the effectiveness and safety of miRNA-derived drugs depends on cellular context and pre-existing genetic and epigenetic lesions due to heterogeneous nature of disease, this area of research needs to be carefully appraised in GBC.

CONCLUSION

miRNAs constitute an important regulator of carcinogenesis. Frequent deregulation of various miRNAs in GBC has been found to affect tumor growth and survival, suggesting miRNAs as promising biomarkers for GBC diagnosis and prognosis. Further, miRNA signature in blood sample represents a future non-invasive diagnostic biomarker for GBC. miRNAs also represent wide-ranging applications as new targets for treatment by inhibition of overexpressed oncogenic miRNAs or inhibition of tumor suppressive miRNAs. The high stability of miRNAs when compared with mRNA molecules in both blood samples and formalin-fixed, paraffin-embedded tissue samples offers a great advantage suggesting miRNAs as a promising approach to ameliorate GBC. However, the number of studies investigating the miRNAs signature in GBC is limited. Therefore, larger well-designed studies with clinical outcome are needed to investigate the complex network of miRNAs in the pathogenesis of GBC.

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ISSN 1007-9327