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Review Article

Implication of miRNAs in the Pathogenesis of Gallbladder Cancer

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Abstract

MicroRNAs (miRNAs) are small non-coding RNAs which regulate key cellular processes through a negative post-transcriptional regulation of their target mRNAs. They can act either as oncogenes or as tumor suppressors or as both, depending on the specific tissue expression. Oncogenic miRNAs act directly on mRNAs from genes with pro-apoptotic or anti-proliferative roles. Conversely, tumor-suppressor miRNAs repress the expression of genes with oncogenic functions. Deregulation of many of these miRNAs has been associated with tumorigenesis in various cancers and recent studies have shown evidences of abnormal miRNA expression in gallbladder cancer. Here, we review our current understanding of the expression changes in tumor-suppressor miRNAs (miR-1, miR-145, miR-135a-5p, miR-26a, miR-34a, miR-335, miR-130a and miR-218-5p) and oncogenic miRNAs (miR-155, miR-20a and miR-182) and its implication in the pathogenesis of gallbladder cancer and their potential as diagnostic and prognostic markers.

Keywords: MicroRNAs; Gallbladder cancer; Oncogenes; Tumor suppressors; Diagnostic markers; Prognostic markers

Biogenesis of miRNAs

MicroRNAs (miRNAs) are endogenous non-coding RNAs that bind to the 3' Untranslated Region (UTR) of a target mRNA, specifically in sequence called MRE (miRNA recognition element) which can be fully or partially complementary. miRNAs are key post-transcriptional regulators of multiple genes and determine the function of the cells under homeostatic and disease conditions [1]. For this reason, are being widely studied as an important family of molecules with promising prospects as diagnostic and prognostic biomarkers and as therapeutic targets [2]. The miRNA genes usually are transcribed by RNA polymerase II or III generating an initial structure, a primary-miRNAs (pri-miRNAs) in the nucleus, with a stem-loop hairpin structure of ~80-nts [3-5]. Mature miRNAs result from cleavage of pri-miRNAs by the Drosha/DGCR8 complex ('microprocessor' complex) to form a precursor miRNAs (pre-miRNA) of a ~60-nts hairpin [6] (Figure 1). Then the pre-miRNA is exported into the cytoplasm by Exportin 5 (XPO5) and Ran-GTP [7]. This pre-miRNA is cleaved by Dicer/TRBP complex generating a miRNA/miRNA* duplex [8]. Finally, one strand of this miRNA duplex binds to the RNA-induced silencing complex (RISC), which carry this strand to target mRNAs, whereas the other strand (miRNA* strand) is degraded [9-11]. However, reports have shown that the temporary string (miRNA*) would have the regulatory capacity, as a mature miRNA [12]. Another processing pathway involves short introns containing miRNA precursors which lack of stem-loop, called "mirtrons". These miRNA precursors are digested via spliceosome [12,13] and are processed in a Drosha- or Dicer-independent manner. Other reports have stated that many miRNAs can be generated from an unusual hairpin structure which is processed by Ago2 instead of Dicer [14].

miRNAs play a role on various biological processes such as differentiation, proliferation and apoptosis [15,16] and control multiple genes involved in cancer. The same miRNA gene can act as tumor suppressor gene or as oncogenes [17,18] due to tissue specificity characteristics. Oncogenic miRNAs act directly on mRNAs from genes with pro-apoptotic or anti-proliferative roles. Conversely, tumor-suppressor miRNAs repress the expression of genes with oncogenic functions. Accumulating evidence indicates that miRNAs display aberrant expression patterns and functional abnormalities in many types of cancers, including gallbladder cancer [19-22].

miRNAs in Gallbladder Tumorigenesis

Gallbladder Cancer (GBC) is the most common malignancy of the biliary tract, representing 80%–95% of biliary tract cancers worldwide [23]. The GBC evolution is asymptomatic in most cases, resulting in a late diagnosis, with low survival [23,24]. There are many reports focused on the genetic and epigenetic alterations in GBC, which involve modifications in the expression of tumor suppressor genes and oncogenes. However, there are few studies focused on miRNA-based epigenetic modifications involved in gallbladder carcinogenesis. Srivastava et al. [25] initially evaluated the effects of three single nucleotide polymorphisms (SNPs) in pre-miRNAs [hsa-miR-146a (rs2910164), hsa-miR-196a2 (rs11614913) and hsa-miR-499 (rs3746444)] according to the GBC risk in a North Indian population, concluding that the genetic polymorphisms in these miRNA may not contribute to GBC susceptibility in the studied population [25]. A second study performed by Kitamura et al. [26], characterized the miRNA expression pattern and investigated potential mechanisms for the therapeutic effects of histone deacetylase inhibitor PCI-24781 on BK5.erbB2 mice, which is a well-established animal model of gallbladder cancer with a high expression of erbB2 under the control of the bovine keratin 5 promotor [26,27]. Several miRNAs were significantly deregulated in BK5.erbB2 mice compared

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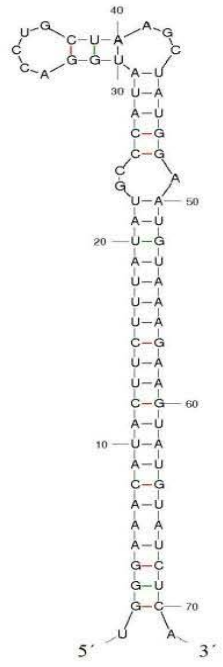

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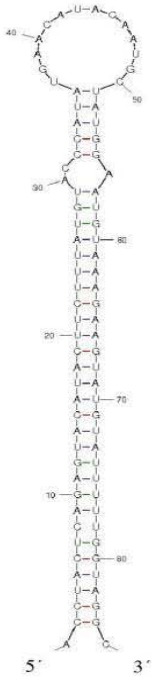

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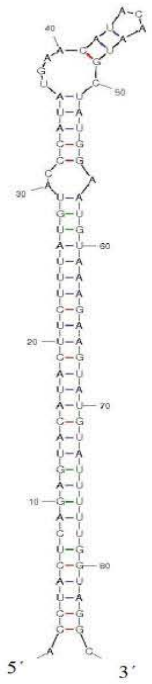

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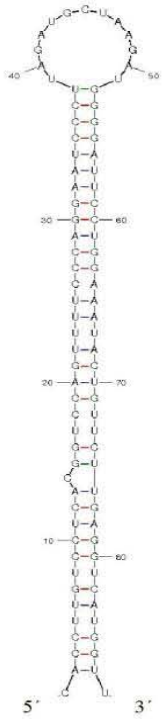

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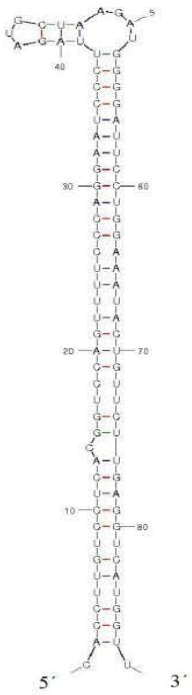

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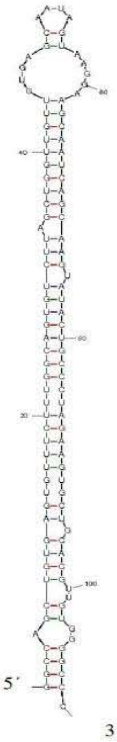

hsa-pre-miR-34a
dG = -50.70 kcal/mol

Figure 1: Examples of miRNAs precursor's structures**.** Images show individual structures and thermodynamic details (dG or ΔG) of some tumor-suppressor miRNA precursors in *H. sapiens* (hsa-pre-miR-1-1, hsa-pre-miR-1-2, hsa-pre-miR-145, hsa-pre-miR-34a). Sequences were obtained from miRBase (www.mirbase.org/) and stem-loop structures were predicted using Mfold software [130].

to normal gallbladder. Nine miRNAs were significantly up-regulated (miR-21, miR-142-3p, miR-142-5p, miR-15b, miR-17, miR-27a, miR-223, miR-96 and miR-106) and thirteen miRNAs were down-regulated (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) [26]. Treatment with PCI-24781 significantly decreased the expression of some of these miRNAs, including miR-21, miR-142-3p, miR-142-5p, and miR-223, which were initially up regulated in GBC. Conversely, PCI-24781 also induced a significant up-regulation in the expression of miR-122, which was down-regulated in GBC [26]. On the other hand, the expression of Dicer and Drosha has been found significantly lower in GBC compared with normal tissue [28]. Furthermore, the lower expression of these enzymes is associated with decreased overall survival of the GBC patients [28], suggesting that aberrant expression of Dicer and Drosha in GBC may be involved in the deregulation of miRNA expression.

All these initial reports suggest that miRNAs may control gene expression in GBC model and play an important role in carcinogenesis of this disease. This review attempts to summarize all the evidence scientific published to date on this topic, in order to understand how the miRNAs expression changes (tumor-suppressor and oncogenic miRNAs role) may be involved in the pathogenesis of GBC (Table 1).

Tumor-Suppressor miRNAs in GBC

miR-1 and miR-145

miR-1 and miR-145 have been extensively studied as potential tumor suppressors in different human tumors such as colorectal cancer [29,30], prostate cancer [31], thyroid carcinoma [32], squamous cell carcinoma of the jaw sine [33], B-cell malignancies [34] and breast cancer [35]. Recently, we used the significance analysis of microarrays (SAM) algorithm to identify a set of 36 miRNAs consistently down regulated in GBC compared to normal gallbladder mucosa. The qRT-PCR analysis confirmed this reduced expression of miR-1, miR-133 and miR-145 ($P < 0.05$) in tumors and GBC cell lines compared to normal gallbladder tissues [36]. The ectopic expression of miR-1 and miR-145 in NOZ cell lines of GBC significantly inhibited cell viability and colony formation ($P < 0.01$) and only miR-1 reduced gene expression of known oncogenes such as the vascular endothelial growth factor A (*VEGF-A*) and AXL receptor tyrosine kinase *(AXL),* suggesting that miR-1 and miR-145 act as tumor suppressor miRNAs in GBC [36]. Interestingly, in a study driven in Chinese population, 23 down regulated miRNAs were identified based on the miRNA chip results obtained from four paired GBC and paracancerous tissues. The miR-1 expression was significantly lower in the GBC tissues compared with the expression of other down regulated miRNAs ($P < 0.001$ and fold change of -170) [37]. Several studies indicate that miR-1 regulates a wide set of genes such as *MET, FOXP1, HDAC4* and *PIM1* in lung cancer [38], *LIM LASP1* and SRSF9 in bladder cancer [39,40], *CCND2*, *CXCR4* and *CXCL12* in thyroid cancer [32]; *PNP* and *TAGLN2* in maxillary sinus squamous cell carcinoma [33], *PTMA* in nasopharyngeal carcinoma [41]; and *FN1* in laryngeal squamous carcinoma [42].

miR-135a-5p and miR-26a

miRNA-135a-5p (miR-135a) and miR-26a have been found as significantly down regulated in GBC tissues from a Shanghai population cohort compared with paracancerous tissues [37,43]. Further, ectopic expression of miR-135a and miR-26 inhibited the proliferation of GBC cells *in vitro* and *in vivo* by directly targeting the very low density lipoprotein receptor (*VLDLR*) and the high mobility group AT-hook 2 (*HMGA2*), respectively [37,43]. The expression of these miRNAs was also correlated with the histologic grade in patients with GBC [37,43]. In addition, the miR-135a-5p–VLDLR axis exerts its function through the activation of p38/MAPK pathway, being implicated in many physiological and carcinogenic processes, such as cell proliferation, cell differentiation, cell death, cell migration, and invasion [37,44].

miR-34a

The miR-34a expression has been found significantly lower in gallbladder tumor tissues than in peritumoral tissues. Further, miR-34a is involved in a decreased colony formation *in vitro,* a decrease in telomere length, and in the inhibition of tumor growth *in vivo,* which

Table 1: Characteristics of tumor-suppressor and oncogenic miRNAs in gallbladder cancer.

Micro-RNA	Up/Down Regulation	Chromosomal location	Mature miRNAs sequences	Number validated targets	Potential target in GBC	Reference
hsa-miR-1	Down	20q13.33 18q11.2	5' uggaauguaaagaaguauguau3'	118	*VEGF-A* *AXL*	[36]
hsa-miR-145-5p	Down	5q32	5' guccaguuuucccaggaaucccu3'	19	Unknown	[36]
hsa-miR-135a	Down	3p21.1	5' uauggcuuuuuauuccuauguga 3'	3	*VLDLR*	[37]
hsa-miR-26a	Down	3p22.2	5' uucaaguaauccaggauaggcu 3'	6	*HMGA2*	[43]
hsa-miR-34a	Down	1p36.22	5' uggcagugucuuagcugguugu 3'	24	*PNUTS*	[45]
hsa-miR-335	Down	7q32.2	5' ucaagagcaauaacgaaaaaugu 3'	3	Unknown	[48]
hsa-miR-130a	Down	11q12.1	5' cagugcaauguuaaaagggcau 3'	7	Unknown	[54]
hsa-miR-218-5p	Down	4p15.31 5q34	5' uugugcuugaucuaaccaugu 3´	4	*BMI-1*	[57]
hsa-miR-155	Up	21q21.3	5' uuaaugcuaaucgugauaggggu 3'	26	Unknown	[63]
hsa-miR-20a	Up	13q31.3	5' uaaagugcuuauagugcagguag 3'	2	*SMAD-7*	[68]
hsa-miR-182	Up	7q32.2	5' uuuggcaaugguagaacucacacu 3'	4	*CADM1*	[76]

Chromosomal Location, sequence and number validated targets were obtained from http://mirecords.biolead.org/index.php and http://www.ncbi.nlm.nih.gov/

Abbreviations: GBC: Gallbladder Cancer; VEGF-A: Vascular Endothelial Growth Factor A; AXL: *AXL* receptor tyrosine kinase; VLDLR: Very Low Density Lipoprotein Receptor; HMGA2: High Mobility Group AT-hook 2; PNUTS: Phosphatase 1 Nuclear Targeting Subunit; SMAD7: Mothers against Decapentaplegic Homolog 7; CADM1: d Cell adhesion molecule1.

was associated with the down regulation of phosphatase 1 nuclear targeting subunit (*PNUTS*) [45]. As known, the telomere biology plays a critical and complex role in the initiation and progression of cancer [46]. Moreover, survival information of 77 patients with GBC revealed that patients with lower miR-34a expression survived significantly less than patients with a higher miR-34a expression ($P < 0.001$). Multivariate survival analysis using cox regression model revealed that miR-34a expression was positively correlated with overall survival in GBC patients [45]. In fact, miR-34a is currently one of the most characterized tumor suppressor miRNAs in a variety of tumors and antagonizes vital processes of tumor aggressiveness such as cell viability, cancer stemness, metastasis and chemoresistance [47].

miR-335

The reduced expression of miR-335 is associated with aggressive clinicopathologic features of GBC, specifically with high histologic grade, advanced clinical stage and positive lymph node metastasis [48]. Furthermore, a reduced expression of miR-335 in GBC patients is associated with poor prognosis and determines an independent prognostic influence factor on overall survival [48]. miR-335 has been identified as a metastasis-suppressor miRNA in cancers and its low expression has a close correlation with cancer development [49-52]. In contrast, over expression of miR-335 may also have an important role in the development of pediatric acute leukemia [53], confirming the dual functions of miRNAs due to tissue specificity of these molecules.

miR-130a and miR-218-5p

miR-130a inhibits proliferation in GBC cell lines and its expression is regulated by HOTAIR's [54], a long non-coding RNAs (lncRNA) with oncogenic properties [55]. lncRNA HOTAIR is involved in specific chromatin remodeling and is a strong predictor for metastasis in some cancers such as breast cancer [56]. A recent publication has shown that the Colon Cancer-Associated Transcript-1 (CCAT1), a 2628-bp lncRNA promotes GBC development via negative modulation of miR-218-5p. *In vitro* assays showed that miR-218-5p module gene expression of polycomb group gene *BMI-1* [57]. miR-130a and miR-218-5p have been found down regulated in several carcinomas and exhibits tumor-suppressive activity [58-61]. However, miR-130 has a pro-angiogenic effect because that down regulates antiangiogenic homeobox proteins GAX (growth arrest homeobox) and HOXA5 [62].

Oncogenic miRNAs in GBC

miR-155

The expression of miR-155 has been found significantly higher in the GBC tissues compared with normal gallbladder. Interestingly, the miR-155 expression is not up regulated in gallbladders with pancreaticobiliary maljunction. A high miR-155 expression was significantly associated with the presence of lymph node metastasis, vessel invasion and poor prognosis. *In vitro* assays showed that aberrant expression of miR-155 significantly enhanced GBC cell proliferation and invasion [63]. Previous reports have suggested that miR-155 is an oncogenic miRNA, which is also over expressed in other human malignancies, including pancreas, colon, glioma, prostate cancers [64-67].

miR-20a

miR-20a is up regulated in GBC and plays a potential role in promoting both cell proliferation and metastasis *in vitro* and *in vivo* through a direct binding to the *SMAD7* mRNA, a potential inhibitor of *TGF-β1* signaling pathway, suggesting that *TGF-β1*/miR-20a/*SMAD7* axis plays an important role in the progression of GBC [68]. Patients with a higher expression of miR-20a exhibited worse overall survival [68]. Moreover miR-20a increase the length and thickness of F-ACTIN microfilaments, a stress fiber regulating cell motility and polarization associated a metastatic property [68].

miR-20a is encoded by the miR-17-92 cluster (miR-17-5p, miR-17-3p, miR-18a, miR-19a, miR-19b and miR-20a) [62], a miRNA polycistron also known as oncomir-1, which is among the most potent oncogenic miRNA genes [69]. For example, in cholangiocarcinoma (CCA), an epithelial cancer within the biliary tree [70], was observed that the over expression of miR-17-92 cluster increase tumor cell proliferation *in vitro* and *in vivo* [71]. Many studies have found that miR-20a is over expressed in the lung cancer [72], glioma [73] and prostate cancer [74], influencing the tumor phenotype in these malignancies. However, other reports have shown that miR-20a is down regulated in cutaneous squamous cell carcinoma and is involved in tumor inhibition [75]. These results suggest that miR-20a could play a role both as oncogene and tumor-suppressor miRNA, similar to miR-335 and miR-130, above-mentioned.

miR-182

miR-182 levels were also significantly up regulated in metastatic GBC patients compared with normal gallbladder tissues, promoting cell migration and invasion by targeting cell adhesion molecule 1 (*CADM1*) [76]. This over expression of miR-182 in GBC cells may be induced by transforming growth factor beta (TGF- β) [76]. Recent publications have reported that miR-182 is deregulated in stomach cancer [77], ovarian cancer [78], breast cancer [79], pancreatic cancer [80] and colorectal carcinoma [81], being involved in carcinogenic processes such as alterations in cell cycle, proliferation, invasion, metastasis and epithelial-mesenchymal transition [77-84]. Furthermore, circulating miR-182 has been detected in clinical specimens such as plasma and serum in pancreatic cancer [80], breast cancer [85] and lung cancer patients [86] with a high specificity.

Other miRNAs with a potential oncogenic role, whose levels are significantly higher in GBC compared to normal tissues, are hsa-miR-196a, hsa-miR-205, hsa-miR-196b and hsa-miR-1290 ($P<0, 05$) [37]. In addition, our research group have shown that miR-92b*, miR-923, miR-149*, miR-513a-5p and miR-765 are over expressed in GBC (unpublished data).

Discussion

The gallbladder cancer is the most common malignancy within biliary tract with remarkable incidence variations around the world [23,87]. The GBC cases are diagnosed in advanced stages, resulting a very poor prognosis [88]. Therefore, it is necessary identify and validate novel markers and therapeutic targets in order to improve the diagnosis, prognosis or treatment for advanced GBC patients. miRNAs are a class of small, single-stranded, non-coding RNA molecules which can act as oncogenes or tumor suppressor genes in human cancers [43,89]. Different studies have reported that several

miRNAs are significantly deregulated in GBC, most of them showing a decreased expression in GBC compared to normal gallbladder tissues (miR-1, miR-145, miR-135a-5p, miR-26a, miR-34a, miR-335, miR-130a and miR-218-5p) and others showing increased expression in neoplastic tissue compared to normal gallbladder tissues (miR-155, miR-20a and miR-182). Interestingly, some of these miRNAs as miR-26 [90], miR-34a [91] and miR-155 [92] also exhibited aberrant expression in CCA. Furthermore, miR-21 that was significantly up regulated in BK5.erbB2 mice model [26] as well as CCA [93], showed a sensitivity of 95% and a specificity of 100%in distinguishing between CCA and normal tissues [93].

The miRNA expression has been correlated with pathologic parameters, according to TNM staging system for GBC (American Joint Committee on Cancer, AJCC, and 7th edition) [94]. The reduced expression of miR-135-5p, miR-26a and miR-335 showed a significant association with TNM stage (stage I + II vs. stage III + IV) [37, 43, 48]. In addition, the reduced expression of miR-335 is associated with positive lymph node metastasis [48]. Otherwise, oncogenic miRNAs (which are over expressed in GBC tissues), were associated with cell invasion in mouse models (miR-182 and miR-20a) [68,76] and enhanced the proliferation and invasion in GBC cell lines (miR-155) [63]. In terms of the evaluation of survival, patients with lower miR-34a and miR-335 expression had poorer survival than patients with a higher expression of these miRNAs, and both were independent prognostic factors of GBC outcomes [45,48]. In contrast, GBC patients with higher miR-155 and miR-20a expression showed a significantly poorer survival [63,68]. However the multivariate survival analysis revealed that only miR-20a was an independent prognostic factor [68]. Different *in vitro* studies demonstrate that ectopic expression of some miRNAs showed a significantly decreased colony formation (miR-1, miR-145 and miR34a) [36,45], an inhibition of cell viability (miR-1 and miR-145) [36], and inhibition of the GBC cell proliferation (miR-135, miR-26 and miR-130a) [37,43,54]. In contrast, inhibitors against miR-155, miR-20a and miR-182 decreased *in vitro* cell proliferation and invasion [63,68,76], suggesting that these miRNAs play a regulating role in the tumorigenesis and progression of GBC.

The scientific evidence indicates that deregulation of miRNA expression could be explained by several mechanisms. Around 50% of genes encoding miRNAs are located at fragile sites of genome and in sites called "cancer associated genomic regions" (CAGRs), which can present Loss of Heterozygosity (LOH), breakpoint zones, and amplification, deletion or mutation regions [95-97]. For example, miR-26a gene is located in 3p23, which is a fragile chromosomal region associated with various human cancers [98]. Although the most of miRNAs are in intergenic regions, several of them are located in intronic regions of known genes and could be co-transcribed, or are located in clusters of miRNAs, transcribed individually or in group from polycistronic sequences (e.g. miR-17-92 cluster, where miR-20a is encoded) [99,100]. A lower percentage of miRNAs are expressed independently with their own promoter regions [101]. Therefore, as the majority of genes, miRNA transcription is regulated by many transcription factors (TP53, MYC, and RAS) in a tissue specific manner [89].

Aberrant DNA methylation in promoter regions also regulate to miRNA gene expression in human cancer [102,103], silencing especially tumor suppressor miRNAs (miR-1 [31,104,105], miR-145 [106,107], miR-26 [108], miR-34a [109-112] and miR-335 [49,113]). In addition, the epigenetic regulation has been demonstrated experimentally in oncogenic miRNAs, such as miR-155 in cell lines of multiple myeloma [114] and miR-17-92 cluster in idiopathic pulmonary fibrosis [115]. Most promoter regions are closely related to CpG islands, however, silencing by DNA methylation does not always require the vicinity of CpG islands, such as the case of miR-199 which is methylated distal to the promoter (without a CpG island) in a cell line of testicular cancer [116]. Other important factor that can also affect the expression and function of miRNAs is related to an inadequate biogenesis, caused by a defect in key enzymes involved in this process (Drosha, Dicer and Exportin 5). The inactivation of Drosha or Dicer results in a significant reduction of miRNAs leading to an aberrant expression in several cancers [117-121]. Dicer and Drosha expression is significantly lower in gallbladder adenocarcinoma compared to non-dysplastic gallbladder epithelia and was significantly associated with lymph node metastasis and decreased overall survival of patients [28], suggesting that aberrant levels of these enzymes may be involved in the deregulation of miRNA expression and consequently in the pathogenesis of GBC. The inactivation of XPO5 also result in the nuclear retention of miRNA precursors [89] but there are not studies about XPO5 expression in GBC.

Conclusion

The multiple genetic alterations found in cancer are associated with numerous structural and functional changes. Although most of the neoplastic processes follow a common pattern, there are specific genes that are directly related to the affected tissue. These alterations are usually acquired during a prolonged time and are result of increased genomic instability which leads to up regulation of oncogenes and suppression of tumor suppressor genes. Thus, during the onset and neoplastic progression, malignant cells become independent from tissue physiological control through gain certain characteristics as own transforming growth signals, evasion of apoptosis, angiogenesis development, unlimited replicative potential, invasiveness (metastasis), the escape of immune response and resistance to certain treatments [122]. Descriptive studies indicate that gallbladder carcinogenesis is a multifactorial process, a product of accumulation of multiple genetic and epigenetic alterations and ambient factors, with a marked difference at each stage of the disease model (metaplasia-dysplasia carcinoma and adenoma-carcinoma) [123,124]. However, information regarding the molecular and genetic alterations in GBC is still scarce. At present the miRNAs emerge as an important family of molecules with promising prospects as biomarkers and therapy targets. As biomarkers, may be useful to assess either the tumor type, progression grade, response to chemotherapy or prognosis much better than traditional gene expression studies, providing important information for physicians and patients. Unfortunately miRNAs has not been evaluated in blood samples of GBC patients. Moreover, currently the design of new cancer treatments based on the molecular and genetic knowledge of the disease has been important in order to complement and enhance the mechanism of action through the combined use of these novel strategies with conventional therapy. This approach would be useful to lessen the adverse effects that may affect the quality of life of patients, mainly because synergistic action may require a reduction in dose,

obtaining a more effective therapy with less side effects [125]. Several studies have evaluated the effect of ectopic expression of miRNA or repression by inhibitors of miRNAs in cell lines and animal models. For example, in hepatocarcinoma cell lines has been reported that the re-expression of miR-1 with hypomethylating agents causes cell cycle arrest and induction of apoptosis [104]. The intratumoral injection of exogenous let-7 miRNA blocked tumor development in mouse models of lung cancer [126] and the inhibition of miR-132 prevents angiogenesis in an orthotopic xenograft mouse model of human breast carcinoma [127]. The first human clinical trial has used LNA-anti-miR-122 (locked-nucleic-acid antisense oligonucleotides) against a highly conserved site in the genome of hepatitis C virus. The results have shown this therapy has a potent anti-viral activity, and currently is being evaluated in a phase II clinical trial [128-130]. Despite this promising result, the efficacy and safety of miRNA therapy should be carefully evaluated because the response depends on the epigenetic and genetic profile of each individual. All these approaches are still at an early stage, but with the development of new technologies, especially improving the specific delivery of tumor-suppressor miRNAs into damaged tissues, this strategy may become an important tool in diagnosis and treatment of this disease.

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