Insights into roles of the miR-1, -133 and -206 family in gastric cancer (Review)

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Abstract. Gastric cancer (GC) remains the third most common cause of cancer deaths worldwide and carries a high rate of metastatic risk contributing to the main cause of treatment failure. An accumulation of data has resulted in a better understanding of the molecular network of GC, however, gaps still exist between the unique bio-resources and clinical application. MicroRNAs are an important part of non-coding RNAs and behave as major regulators of tumour biology, alongside their well-known roles as intrinsic factors of gene expression in cellular processes, via their post-transcriptional regulation of components of signalling pathways in a coordinated manner. Deregulation of the miR-1, -133 and -206 family plays a key role in tumorigenesis, progression, invasion and metastasis. This review aims to provide a summary of recent findings on the miR-1, -133 and -206 family in GC and how this knowledge might be exploited for the development of future miRNA-based therapies for the treatment of GC.

Contents

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1. Introduction

Gastric cancer (GC), despite declining to the fifth most commonly diagnosed malignancy, remains the third most common cause of cancer deaths worldwide and thus a significant global cancer burden (1). Patients typically present with disease that appears at an advanced stage accompanied by extensive invasion and lymph node involvement. Limited therapeutic methods, the development of drug resistance, local recurrence and distant metastasis are all challenging the prognosis of GC patients.

miRNAs. In recent years, we have seen significant progress in understanding that miRNAs (miRs) act as major intrinsic factors of gene expression. They have extended our knowledge of how morphogenesis and differentiation are regulated in cellular processes. miRs are single-stranded, 19-22 nucleotide long molecules, and are evolutionarily conserved across species (2,3). To date, as many as 2588 miRs encoded by the human genome have been confirmed (4,5), including the miR-1, miR-206 and miR-133 family, which is observed playing a crucial role in myogenesis. miRs can be transcribed by ribonuclease II (RNase II) or ribonuclease III (RNase III) into primary miRs (pri-miRs), several kilobases in length, which are cleaved by the RNase III enzyme Drosha into shorter hairpin structures called precursor-miRs (pre-miRs) that are 70-100 bases long (6). Pre-miRs have a short stem and a two-nucleotide 3' overhang which is recognised by the nuclear transport receptor exportin 5 (EXP5), and exported from the nucleus to the cytoplasm by Ran-GTP- and EXP5-dependent mechanisms (7,8). In the cytoplasm, another RNase III enzyme, Dicer, further processes the pre-miR into a miR-miR* duplex approximately 22 bases long (9). The double-stranded RNA duplex is then loaded into the Argonaute (AGO) protein and further processed, generally, causing the miR* to be expelled, which results in a functional RNA-induced silencing complex (RISC), which can base pair to a target mRNA, mostly through seed-matched sites located in 3' untranslated regions (3'-UTR)

of the mRNA, and induce its degradation or silencing (10-13). miRs have numerous high and low affinity targets, averaging 300 conserved targets per miRs family (11). Although the effects of an individual miR on a specific mRNA target may be relatively modest, the combined effects of a miR on multiple targets functioning within a common pathway can be synergistic, and make fine-scale adjustments on cell proliferation, motility, apoptosis and cell-fate decisions (14-17).

2. miRs in GC

miRs exhibit varied expression patterns, from uniform during development to relatively stage-specific and/or tissue specific (2,3), which suggests miRs profiling could distinguish cancer from normal tissues or between different cancers (18-21). miRs are now increasingly being examined by miRs microarray and bioinformatics to analyze their correlation with progression and prognosis of GC.

High-throughput studies on miRs in GC (Table I). In 160-paired samples of non-tumour mucosa and cancer, 22 microRNAs were upregulated and 13 were downregulated in GC (22). Liu *et al* screened miR expression in serum samples pooled from 20 patients and 20 controls by Solexa sequencing, and found 19 serum miRs were markedly upregulated in the GC patients compared to the controls. The qRT-PCR analysis further identified a profile of five serum miRs as a biomarker for GC detection (23). Of note, Zhou *et al* using qRT-PCR based Exiqon panel analysed a total of 33 miRs abnormally expressed in GC patient serum, and identified a new five-miR signature in the peripheral plasma which was supposed to serve as a non-invasive biomarker in detection of GC (24). In the study of Lo *et al*, the signature of aberrant miRs expression was established by screening and analysis using bioinformatics in Taiwanese patients (25). Kim *et al* further identified upregulated miRs associated with chemosensitivity (26). Using both frozen tissue samples and fresh blood samples, Yan *et al* confirmed 7 upregulated and 5 downregulated miRs that could be used to discriminate between GC with and without recurrence (27).

Yu *et al* analyzed the global miR expression profiles of 9 gastric cancer cell lines and 6 normal gastric mucosa lines using miR microarrays. Seventeen miRs were upregulated in gastric cancer cell lines and 146 miRs were downregulated compared to normal gastric mucosa. To validate the microarray findings, qPCR was performed on 9 gastric cancer cell lines, 6 normal gastric mucosa, and a further 40 gastric cancer tissues and matched adjacent non-cancerous tissues for 41 candidate miRs. The expression levels of the 41 miRNAs using qPCR showed a great deal of variation when compared to microarray data, indicating the high heterogeneity of cancer tissues relative to cancer cell lines (28). Chen *et al* demonstrated that, apart from the commonly altered miRs, GC also has a specific miR expression pattern different from oesophageal adenocarcinoma (20). Among these studies, miR-1, miR-133 and miR-206 are consistently deregulated (18-20,22-27,29,30) and associate with histology pattern (22), tumour stage (23), chemosensitivity (26) and progression (23). In the molecular classification of GC set by The Cancer Genome Atlas (TCGA) datasets, miRs from

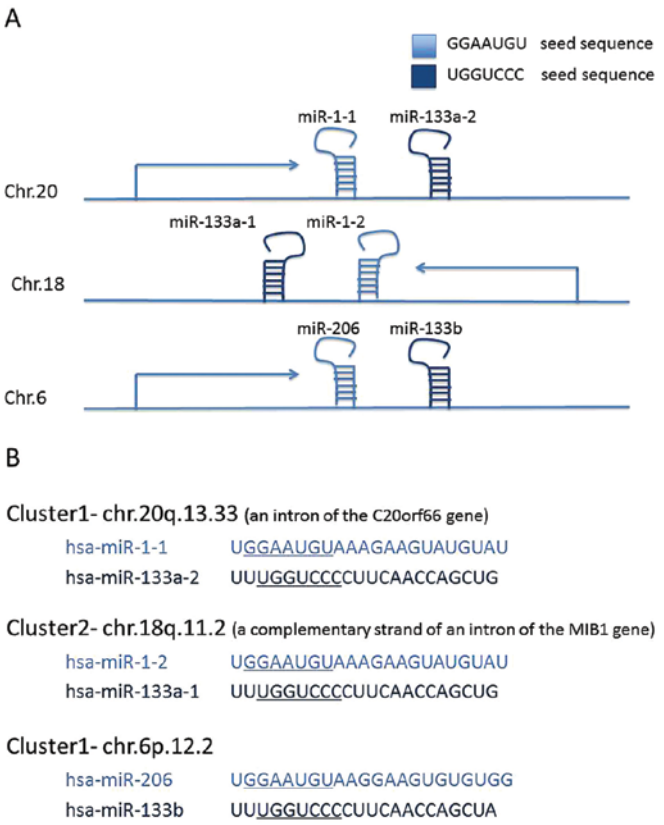

Figure 1. Genomic location and base sequence of the miR-1, -133 and -206 family. (A) The miR-1, -133 and -206 family is located at three different clusters on chromosome 20, 18 and 6. (B) Sequences of the miR-1, -133 and -206 family. The miR-1, -133 and -206 family is divided in two functional groups by their seed sequence: miR-1/206 and miR-133a/133b. [Adapted from Hilmarsdottir *et al* (38)].

295 GC tissues and 33 adjacent non-malignant samples were sequenced, and according to the heatmap analysis, the miR-1, -133 and -206 family was among the most commonly and significantly downregulated miRs (31). In the remainder of this review, we will discuss the functional role of the miR-1, -133 and -206 family with particular emphasis on GC. We will also discuss the expression and regulation of the miR-1, -133 and -206 family in GC, and their potential roles in clinical application.

miR-1, -133 and -206 family. The miR-1, -133 and -206 family was initially discovered through their role in the direction of the development of mammalian skeletal and cardiac muscles. Recent studies on cancer illustrate their deregulation in cancer development, in which typically they function as tumour suppressors, with some evidence of their oncogenic role in different cell environments (35,36).

The miR-1, -133 and -206 family is located at three different loci at chromosomes 20q13.33 (miR-1-1/miR-133a-2), 18q11.2 (miR-1-2/miR-133a-1) and 6p12.2 (miR-206/miR-133b) (Fig. 1A) (36). The two mature miR-1 isomers have identical sequences, as do the two miR-133a isomers. The mature miR-133 isomers (A and B) are also highly similar, differing only at the 3'-terminal base, with miR-133a-1/2 terminating G-3' and miR-133b with A-3', respectively (37). The miR-206 sequence differs from the miR-1 sequence

Table I. Deregulated expression of miRs in GC.

Refs.	Upregulated miRs	Downregulated miRs
Darnet *et al* (30)	miR-135, miR-215	miR-29c, miR-204, miR-664, miR-1501, miR-148a,
Yu *et al* (28)	miR-196a, miR-196b, miR-18a*, miR-106a, miR-18b, miR-93	miR-451, miR-495, miR-409-3p, miR-497, miR-133b, miR-136, miR-29c
Zhou *et al* (24)	miR-185, miR-20a, miR-210, miR-92b, miR-25	
Wu *et al* (32)	miR-224, miR-424p, miR-130a, miR-224*, miR-452, miR-181a, 139b-5p	miR-3127-5p, miR-1287, miR-4713-5p
Kim *et al* (26)	miR-25, miR-106b, miR-93, miR-503, miR-18a, miR-224, miR-451, miR-18b, miR-17-5p, miR-486-5p, miR-144, miR-552 *et al*	miR-146a, miR-133a, miR-133b, miR-1, miR-625, miR-375, miR-195 *et al*
Yan *et al* (27)	miR-335, miR-133a, miR133b, miR-128b, miR-429, miR-194, miR-375	miR-373, miR-19a, miR-142-5p, miR-142-3p, miR-32
Chen *et al* (20)	miR-142-3p, miR-142-5p, miR-146a, miR-146b-p, miR-155, miR-192, miR-194, miR-20a, miR-21, miR-214, miR-215, miR-223, miR-342-3p, miR-765	miR-143*, miR-145, miR-145*, miR-148a, miR-203, miR-31, miR-365, miR-375, miR-451
Liu *et al* (23)	miR-1, miR-20a, miR-27a, miR-34, miR-423-5p	
Lo *et al* (25)	miR-135b, miR-21, miR-189, miR-222, miR-221, miR-187, miR-370, miR-125b	miR-27a, miR-181c, miR-200c, miR-130b, miR-ley-7i, miR-30e, miR-218, miR-141, miR-26a, miR-let-7d, miR-182, miR-29a, miR-148a, miR-199b, miR-135a, miR-133b, miR-199b, miR-135a, miR-191, miR-30d, miR-139, miR-26b, miR-let-7e, miR-338, miR-142-5p
Pennarun *et al* (33)	miR-10b, miR-21, miR-223, miR-338	miR-let-7a, miR-126, miR-30a-5p
Ueda *et al* (22)	miR-181d, miR-181a-1, miR-181s, miR-181b-1, miR-21, miR-25, miR-93, miR-17-5p, miR-106b, miR-20a, miR-19b-1, miR-224, miR-18a, miR-135b, miR-19a, miR-345, miR-191, miR-181a-2, miR-181b-2, miR-19a, miR-135a-2, miR-19b2	miR-148b, miR-375, miR-29b-1, miR-29c, miR-152, miR-218-2, miR-451, miR-30d, miR-30a-5p, miR-30d, miR-30c-1, miR-422b, miR-29b-2, miR-30c-2
Volinia *et al* (18)	miR-223, miR-21, miR-103-2, miR-92-2, miR-25, miR-191, miR-221, miR-125b-2, miR-103-1, miR-214, miR-222, miR-125b-1, miR-100, miR-107, miR-92-1, miR-192, miR-23a miR-215, miR-7-2, miR-138-2, miR-24-1, miR-99b, miR-24-2	miR-218-2, miR-136, miR-212prec, miR-96, miR-138-2, miR-33b
Tchernitsa *et al* (34)	miR-222, miR-25, miR-106b, miR-21, miR-107, miR-103, miR-145, miR-7, miR-214, miR-30b, miR-93, miR-24, miR-143, miR-320, miR-92, miR-125b, miR-27a, miR-23b, let-7a, let-7b	miR-146a, miR-148a

by four nucleotides. Due to their close locations at distinct loci, miR-1/133a, miR-206/133b are constituted as clustered miRNAs. Since the seed sequence is the determining base sequence that decides which mRNA is targeted and degraded. miR-1-1, miR-1-2, miR-206 (miR-1/206) and miR-133a-1, miR-133a-2 and miR-133b (miR-133a/133b) are functionally classified into two groups based on their seed sequence (Fig. 1B).

miR-1, -133 and -206 expression profiles in GC. Changes in the expression of miR-1, -133 and -206 have been documented in various types of cancer, including cancer of the lung (39-41), breast (42,43), prostate (44-46), colon (47,48), oesophagus (49,50) and hepatocarcinoma (51).

miR-1. Several studies have shown that miR-1 was significantly downregulated in GC cells and tissue samples when compared to the adjacent non-tumour tissues (20,26,52,53). Through microarray, Kim *et al* examined miR-1 expression in biopsy samples collected prior to chemotherapy, from 90 gastric cancer patients who were treated with cisplatin/fluorouracil (CF) and from 34 healthy volunteers, was downregulated in GC by more than four-fold, the result was also confirmed by qPCR. Further analysis of miRNA predictors for response to CF therapy showed that miR-1 was one of 37 miRNAs unique to the chemosensitivity signature (26). Chen *et al* applied 2 independent microarray platforms in 3 advanced gastric adenocarcinomas (stages III and IV) and 3 non-tumour histologically normal tissue samples, and also found miR-1

was among the most significantly down-regulated miRs (20). Analyzing data from the TCGA database, miR-1 was widely suppressed across EBV, Genome Stable (GS) and Chromosome Instability (CIN) three different subtypes of GC (EBV subtype typically with PIK3CA mutation, GS subtype characterized by remarkable mutations of RHOA and CDH1, and CIN subgroup featured with obvious TP53 mutation and RTK-RAS mutation). Tsai *et al* demonstrated downregulation of miR-1 directly modulated endothelin-1 (END1) expression in GC, and promoted cell growth, metastasis, angiogenesis, and ultimately suppressed apoptosis. Transfecting GC cell lines with miR-1 plasmids reduced cell proliferation and clonogenic survival of GC cells (52). Han *et al* using immunoblotting confirmed MET was a direct target for miR-1 in GC and transfection of miR-1 mimics exhibited the same negative regulation on cell proliferation and motility as silencing MET expression (53). Taken together, miR-1 was downregulated in GC, and overexpressed miR-1 in GC cells can inhibit cell growth, clonality and migration ability. However, its correlation with clinicopathological characteristics is not yet explained, and the molecular mechanism remains to be elucidated.

miR-206. Unlike miR-1, few microarray studies showed alteration in miR-206 expression in GC patients. Upregulation of miR-206 differed from miR-1 and tended to serve as a chemoresistance indicator (26). However, when detected alone, repressed miR-206 expression in GC tissues and GC cell lines are consistent in several studies (54-58). Lin *et al* compared miR-206 expression in primary GC tissues with those in normal adjacent mucosa from 30 patients, miR-206 expression was found to be significantly decreased in 30 of the GC samples (54). Furthermore, Yang *et al* validated this observation in a larger population which included 98 paired samples, and clinicopathological analysis revealed that tumours with low miR-206 expression were more prone to having lymph node metastasis (P=0.01), presence of venous invasion (P=0.008), and hematogenous recurrence (P=0.01), and tended to occur in a worse stage (P=0.03) than the tumours with a high miR-206 expression. GC patients with low miR-206 expression also had shorter overall survival than those with a high miR-206 expression (P=0.02). Multivariate analysis showed that miR-206 expression was an independent prognostic factor for patients with GC as well, which strongly suggested that the downregulation of miR-206 was significantly linked with tumour progression and its potential role served as a prognostic marker in gastric cancer (55). Correlation between downregulation of miR-206 with lymph node metastasis, local invasion, and advanced TNM staging was also found by Ren *et al* via qPCR detection. *In vitro* and *in vivo* studies also demonstrated miR-206 may mediate the anti-metastatic effect by targeting metastasis regulatory genes STC2, HDAC4, KLF4, IGF1R, FRS2, SFRP1, BCL2, BDNF, and K-ras, which were drastically down-regulated by stable expression of exogenous miR-206 in GC cell lines (56). Zhang *et al* showed miR-206 expression in metastatic lesions was more decreased than those in the corresponding primary tumour samples (57). Presented analyses proved that miR-206 acted as a tumour suppressor in GC, and considering its role in predicting prognosis of GC patients, strategies regarding the regulation of miR-206 in GC treatment might be useful.

miR-133. Data mining in miRNomes across TCGA datasets showed miR-133a and miR-133b as well as miR-1 were consistently downregulated in GC (31). This result was confirmed in GC cell lines and primary GC tissues by both microarray and qPCR methods. The level of miR-133 in GC and corresponding non-tumour tissues was detected in three different groups of GC patients independently (59-61). Results further revealed that miR-133 reduction is more likely to perform worse in tumour size, invasion depth and peripheral organ metastasis. Dysfunction of miR-133 was an independent prognosis factor for overall survival (60,61). Moreover, by luciferase assay, miR-133 was proved to target 3'UTR of EGFR and HER-2, which may cut cell growth signals off, and inhibits cell growth ultimately promoting apoptosis (59). These related research results of miR-133 in GC as a whole have elucidated a novel mechanism for oncogene inhibition by miRNA-mediated pathways and offer new avenues for GC treatment.

Circulating miRs in GC patients. Although data has helped to form a better understanding of the alteration of microRNAs in GC samples as well as in patient serum, the consistency between tissues and blood samples, the source of generation and storage of circulating miRs, and their roles in the mechanism of GC still need further confirmation.

Circulating microRNAs were previously reported to be stored in exosomes and released from normal tissues or tissues affected by diseases (62-64). Containing miRs, exosomes were secreted into circulation and transferred to target cells in either normal or pathologic conditions (65). Therefore, the finding of tumour-derived miRs in plasma or serum could support the application of circulating miRs in disease early-detection since circulating miRs are protected from degradation by ribonucleases in blood and thereby can be stably detected (64), and could serve as low-invasive useful biomarkers for various cancers (66-68), including GC (69,70). However, these researchers showed inconsistent results on the use of miRs for GC detection (71).

Liu *et al* (23) identified a profile of five serum microRNAs (miR-1, -20a, -27a, -34, and -423-5p) as biomarkers for GC detection by Solexa sequencing. Huang *et al* collected 82 blood samples from patients who were diagnosed with metastatic or recurrent GC before first-line chemotherapy. After performing qRT-PCR assay, they demonstrated that patients with higher serum miR-1 expression levels tended to have a higher rate of liver metastasis. Patients with higher serum miR-1 expression levels also showed a high potential of chemoresistance, with the partial response rates of 11.1%, whilst those in the patients with low miR-1 expression was 23.1% (P=0.048) (72). However, Cai *et al* analyzed 90 plasma samples from GC patients randomly divided into training and testing groups, the results did not show any aberrant conditions for miR-1 (73). Furthermore, in the study of Liu *et al* (60), 305 cases of diagnosed gastric adenocarcinoma from TCGA data set were enrolled to detect miR biomarkers for GC diagnostic and prognostic purposes. The results showed miR-133b, miR-133a-2, and miR-1-2 levels were significantly negative related with race, tumour pathology, and tumour stage (P<0.05). Therefore, the feasibility of using circulating microRNAs for the early detection or for predicting chemotherapy effect and prognosis of GC remains to be established.

3. miR-1, -133 and -206 are regulated by both transcription and by epigenetic regulation

Studies have identified a number of transcription factors that positively or negatively regulate miR-1, -133 and -206 expressions. Independent upstream enhancers have been identified for each pair of genes, and these independent enhancers allow the different isomer genes to be independently expressed under cell specific regulation. MEF2 and EVI1 were reported as enhancers to regulate mir-1-2/133-1-a expression (74,75). Either KLF4 or AGO2 may serve as an enhancer acting on the promoter zone of the miR-206 gene separately (76,77). The myogenic transcription factors myogenin and myogenic differentiation 1 (MyoD) (78,79), as well as Carm1/Prmt4 (80), bind to regions upstream of the miR-1 and miR-133 stem loop, thereby providing a molecular explanation for the observed induction during myogenesis. However, activation of HMOX1 (81) or NRF2 (82) signalling attenuates miR-1 and miR-206 expression, promoting cellular proliferation and tumorigenesis. Although the mTOR (83) and the ERK1/2 (84) signalling pathways negatively regulate expression of miR-1 and miR-133 indirectly in myogenesis, their functions in cancer need further investigation.

In recent years, epigenetic factors such as DNA methylation and histone modifications have increasingly been linked to regulation of the miR-1, -133 and -206 family. Datta *et al* showed in 2008 that epigenetic drugs 5-azacytidine (DNA hypomethylating agent) and/or trichostatin A (histone deacetylase inhibitor) differentially regulated expression of a few miRs, particularly miR-1-1, in hepatocellular carcinoma (HCC) cells. The CGI spanning exon 1 and intron 1 of miR-1-1 was methylated in HCC cell lines and in primary human HCCs but not in matching liver tissues. The miR-1-1 gene was hypomethylated and activated in DNMT1-/- HCT 116 cells but not in DNMT3B null cells, indicating a key role for DNMT1 in its methylation (85). DNA methylation at the miR-1-1/133a-2 promoter correlated highly with invasive capacity of colorectal carcinoma (CRC) cell lines and played a critical role in colorectal cancer metastasis by silencing TAGLN2 (86). Tsai *et al* demonstrated that DNA hypermethylation contributed to the silenced miR-1 expression in GC cells (52).

Recently, adding 5-Azacytidine, histone methylation inhibitor DZNep or histone deacetylation (HDAC) inhibitor SAHA in GC cell culture respectively, Liu *et al* found that added DZNep and SAHA treatment consistently increased the expression of miR-133b/a-3p in GC cell lines. A ChIP assay further quantified the histone epigenetic modification levels in genomic regulatory regions of miR-133b and miR-133a-1. GC cell lines demonstrated reduced levels of H3K4me3 and H3 acetylation in miR-133a-1 promoter region, both linked to transcriptional activation; whereas levels of H3K27me3, linked to transcriptional repression, in miR-133a-1 promoter region, were significantly upregulated in GC cell lines (60).

In physiological muscle differentiation, miR-1, -133 and -206 influence a plethora of cellular cues, leading to cell cycle arrest and terminal differentiation by silencing the expression of Pax7, the early activator of myogenic commitment, or by affecting histone deacetylase-4 (HDAC4) and DNA polymerase-α (87). It is widely accepted that inappropriate deacetylation by the HDAC family, including HDAC4, is a mechanism leading to increase in growth rate and cellular proliferation (88). However, HDAC4 playing out its DNA binding function is Mef2c- and Mef2d-dependent. Notch3 is paradoxically upregulated during the early stages of differentiation by an enhancer that requires both MyoD and activated Notch1, while Notch3 itself strongly inhibits the myogenic transcription factor Mef2c, which induces microRNAs miR-1 and miR-206 (89). Noteworthy, Notch3 and HDAC4 have been confirmed as direct targets of miR-1 and miR-206 (90-92). Singh *et al* found that loss of NRF2 decreased the expression of the HDAC4, forced overexpression of HDAC could repress expression of miR-1 and miR-206, which function as a regulatory feedback loop that repressed HDAC4 expression (82). Moreover, Nasser *et al* found that repressed miR-1 was also activated in lung cancer cells upon treatment with a histone deacetylase inhibitor (91). Although only a few studies have shown the regulation of the miR-1, -133 and -206 family in cancer, they do suggest these factors are executing a vital role in maintaining levels of miR-1, -133 and -206 in cancer cells. In summary, epigenetic control of miR expression, including the miR-1, -133 and -206, is an important tool for the cells to acquire correct fate decision. Transcription factors together with epigenetic modulation demonstrate the complex network of factors controlling the miR-1, -133 and -206 family. In addition, the interactions of miR-1, -133 and -206 with their targets show large amount of complexity of the reciprocal communication between the miR-1, -133 and -206 family and their regulators and targets.

4. Target genes and pathways involved in the miR-1, -133 and -206 family regulation in GC

Online databases, such as TargetScan, and miRWalk, provide plausible targets of the miR-1, -133 and -206 family and their involvement in variable effects in signal pathways. But these computational target genes are known to show false-negative and false-positive results when compared to those results from laboratory techniques (93). miRTarBase (94), a new database, collected miRNA-target interactions that are validated experimentally by reporter assay, western blot, microarray and next-generation sequencing experiments. According to its collections, the miR-1, -133 and -206 family may regulate several pathways in cancer, such as DNA replication, cell cycle, cell junction, p53 and VEGF signalling pathways. In GC, MET, which is a major participant in regulation of cell growth, migration and clonogenic survival, was twice confirmed to have a negative correlation with both miR-1 (53) and miR-206 (95), their direct interactions elucidated by reporter assay were reported in lung cancer (91) and rhabdomyosarcoma (96). Zhang *et al* explained downregulated miR-206 enhanced MET expression via upregulation PAX3 (57), and miR-206-PAX3-MET signalling is critical to GC metastasis (57).

Another study proved miR-206 targeted cyclinD2 (CCND2) directly, downregulated miR-206 lead to increased CCND2 level, thus promoting cell growth and colony forming ability in GC cells with a G0/G1 cell cycle arrest abolished. Gain of function studies revealed that miR-206 reduced GC cell proliferation at least partially through targeting CCND2 (97). Shi *et al* (58) detected miR-206 and CCND2 mRNA expression levels by qRT-PCR in 220 match-pairs

of GC and adjacent non-cancerous tissues, and showed that the expression levels of miR-206 and CCND2 mRNA were, respectively, reduced and markedly elevated in GC tissues, when compared with the adjacent non-cancerous tissues (both P<0.001). Notably, the expression levels of miR-206 in GC tissues were negatively correlated with those of CCND2 mRNA, significantly (r= -0.463, P<0.001). Further analyses displayed that low miR-206 expression and high CCND2 expression, alone or in combination, were all significantly associated with great depth of invasion, positive lymph node and distant metastases, and advanced TNM stage of GC (all P<0.05). The researchers also found that the overall survivals of the patients with low miR-206 expression and high CCND2 expression were, respectively, shorter than those with high miR-206 expression and low CCND2 expression. In addition, miR-206-low/CCND2-high expression was associated with a significantly worst overall survival of all miR-206/CCND2 groups (P<0.001). Furthermore, multivariate analysis identified miR-206 and/or CCND2 expression as independent prognostic factors for overall survival in patients with gastric cancer (58).

Cell division cycle 42 (CDC42), an important member of the Ras homolog (Rho) family, also known as PAK activating factor, is considered to be involved in regulating cell cycle progression, migration, cell cytoskeleton organisation, and cell differentiation. A study demonstrated that CDC42 was a direct and functional target gene of miR-133. Downregulation of miR-133 contributed to elevated expression of CDC42, since a body of evidence indicates that CDC42/PAK pathway plays an important role in tumour growth, invasion and metastasis, as a target of miR-133, overexpression of miR-133 downregulated CDC42 expression and PAK activation, and inhibited cancer cell proliferation and migration (61).

Restoration of miR-133b/a-3p expression suppressed cell proliferation and promoted cell apoptosis as observed in the study of Liu *et al* (60), to explain this phenomenon, after exploring the putative target of miR-133 using TargetScan database, Mcl-1 and Bcl-xL 3'-UTR were assembled into the XbaI site of the pGL3-promoter construct, luciferase assay confirmed that miR-133 could directly bind to 3'-UTR of Mcl-1 and Bcl-xL, and the knock-down of Mcl-1 and Bcl-xL markedly suppresses tumour growth (60).

Taken together, these data imply that the miR-1, -133 and -206 family functions as pleiotropic modulators of cell proliferation, invasion and cell cycle arrest by targeting various genes in GC. Based on computational analysis of the selective maintenance or avoidance of miRNA complementary sites during evolution and experimental identification of messages destabilised or those preferentially associated with argonaute proteins in the presence of a miRNA, large-scale approaches for studying the regulatory effects of miRs have revealed important insights into target recognition and function (98). However, only a few of these gene expression changes have been explained by predicted direct binding of the miR-1, -133 and -206 family to corresponding mRNAs, suggesting that the majority of these proteomic effects may result indirectly. Thereby, with the aid of '*in silico*' data, further studies of the miR-1, -133 and -206 family in GC are warranted due to their potential ability in suppressing and inhibiting cancer cells.

5. Conclusions

The miR-1, -133 and -206 family has been found to be repressed by hypermethylation of promoter or negatively regulated transcription factors in GC. Their deregulation results in general change in gene expression buried in diverse pathways directly or indirectly, and affect cell growth, migration, cell cycle arrest and apoptosis to a variable extent. The miR-1, -133 and -206 family may serve as biomarker for GC diagnosis, progression, prognosis and potential therapeutic targets. By increasing our understanding of the functional role of miR-1, -133 and -206, their roles in suppressing tumorigenesis and metastasis have been evidenced, however, more efforts are required to illuminate the mechanism behind these effects before early detection, or therapy for knocking-in or -out these miRs, are performed.

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