Dysregulation and functional roles of miR-183-96-182 cluster in cancer cell proliferation, invasion and metastasis

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Keywords: miR-183-96-182 cluster, cancer development, cancer progression, metastasis, prognosis

Received: November 17, 2015   Accepted: March 31, 2016   Published: April 12, 2016

ABSTRACT

Previous studies have reported aberrant expression of the miR-183-96-182 cluster in a variety of tumors, which indicates its’ diagnostic or prognostic value. However, a key characteristic of the miR-183-96-182 cluster is its varied expression levels, and pleomorphic functional roles in different tumors or under different conditions. In most tumor types, the cluster is highly expressed and promotes tumorigenesis, cancer progression and metastasis; yet tumor suppressive effects have also been reported in some tumors. In the present study, we discuss the upstream regulators and the downstream target genes of miR-183-96-182 cluster, and highlight the dysregulation and functional roles of this cluster in various tumor cells. Newer insights summarized in this review will help readers understand the different facets of the miR-183-96-182 cluster in cancer development and progression.

INTRODUCTION

microRNA (miRNA) is a small non-coding RNA molecule (containing about 22 nucleotides) that silences cognate target genes via base-pairing with complementary sequences within 3’UTRs (sometimes 5’UTRs or coding regions) in corresponding mRNAs, resulting in inhibition of translation or mRNA degradation [1]. miRNA is involved in various biological processes, including cell proliferation, apoptosis, metabolism and differentiation. miR-183-96-182 cluster is a highly conserved miRNA cluster [2]. Members of this cluster are located within a 5-kb region on human chromosome 7q32.2 [3], transcribed in the same direction from telomere to centromere, and have similar biological functions in some of the closely related signaling pathways.

The transcriptional start site (TSS) of miR-183-96-182 cluster has not yet been confirmed. Several studies have suggested its localization in the 5207, 5200, or 5068 base upstream of miR-183 precursor [4-6]. Tang et al. have suggested that the potential TSS of miR-183-96-182 cluster may be localized at the 5112 site upstream domain of miR-96, which contains seven binding domains of β-Catenin/TCF/LEF-1 complex [7]. Additionally, previous reports have indicated that three TGF-β response elements at 11519-9069 region upstream domain of miR-182, can directly interact with Smad2/Smad4 complex [8]. It is known, that many upstream regulators, including HSF2, β-catenin/TCF/LEF-1, TGF-β, SP1, P53, growth hormones, Akt/FOXP3, and MYOD increase the expression of miR-183-96-182 cluster [9, 19-22]. Hypoxia and/or starvation are known to up-regulate miR-96/miR-182 expression, and miR-183/miR-182 increases the expression of hypoxia inducible factor 1α (HIF-1α) [23-27]. Thus, the relationship between miR-183-96-182 cluster and hypoxia or starvation still needs to be investigated.

While investigating its regulatory effect on the downstream target genes, the miR-183-96-182 cluster was
discovered as being a regulator of tumor development, the nervous system and the immune system [2, 28-34]. Recent studies have documented localization of some tumor-related genes, such as CDK6, BRAF, and c-MET at the upstream/downstream domain of miR-183-96-182 cluster [23, 35, 36], suggesting that these genes might be regulated to process similar functions of tumor-related molecules. Furthermore, over-expression of miR-183-96-182 cluster has been described in most malignant tumors including, hepatocarcinoma [37-39], esophageal cancer [40], gastric carcinoma [7], prostate cancer [41], bladder cancer [42, 43], upper urinary tract urothelial cancer [44], colon cancer [45-47], lung cancer [48], breast cancer [3, 49], and chronic myeloid leukemia [50], indicating that it may function as an oncogene cluster. In contrast, miR-183-96-182 cluster functions as a tumor-suppressor gene with down-regulation in pancreatic cancer [51] and melanoma [52] have been documented. In addition, some recent studies have reported some contradicting features exhibited by the miR-183-96-182 cluster in gastric carcinoma [53, 54] and lung cancer [55-58].

The available evidence, thus, suggests much variability in the role played by the miR-183-96-182 cluster in tumorigenesis, tumor progression and metastasis. In this review, we profile the dysregulation and functional roles of the miR-183-96-182 cluster during tumorigenesis in various tumor cells, and its prognostic relevance in clinical settings. The outline of this paper is provided in Appendix 1-1.

MATERIALS AND METHODS

In this review, we performed an online search of articles published from January 2000 to March 2016 in Pubmed (http://www.ncbi.nlm.nih.gov/pubmed). We used the following query: (miR-96 OR miR96 OR microRNA96 OR miR-183 OR miR183 OR microRNA183 OR miR-182 OR miR182 OR microRNA182 OR miR-183-96-182 OR miR-183/96/182). Only English language articles were included. A total of 620 records were retrieved. We then reviewed the titles and abstracts, and eliminated duplicate and irrelevant articles. Eventually, 155 full-length articles were included in this review.

RESULTS AND DISCUSSION

miR-183-96-182 cluster in cancer cell proliferation

miR-183-96-182 cluster promotes cancer cell proliferation

For examining the role of miR-183-96-182 cluster in cell proliferation, the relation between miR-96 and the members of forkhead box protein (FOX) family has been investigated. FOXO, a subfamily of FOX family that includes FOXO1, FOXO2, FOXO3 and FOXO4, was found to be associated with cell apoptosis. Recent studies have demonstrated that FOXO can activate Bim and p27kip1, resulting in increased cell apoptosis and cell cycle inhibition [59, 60]. In 2009, Guttilla et al. found coordinated repression of FOXO1 by miR-96, miR-182 and miR-27a in breast cancer cells [49]. Targetscan prediction revealed three members of the FOXO protein family, including FOXO1, FOXO3 and FOXO4 as potential targets of the miR-183-96-182 cluster. However, only FOXO1 and FOXO3 have been confirmed by previous studies [16, 35, 49, 61-65], in various types of cancers such as, prostate [63, 66, 67], bladder [43, 68], colorectal [62], breast [69], lung [61], lymphoma [64], and endometrial carcinoma [70] (Table 1). Additionally, recent studies have indicated that miR-182 promotes cell proliferation and tumor invasion by targeting FOXF2 [71, 72], a known inhibitor of MPPs and WNT5A [73, 74].

HMG-box transcription factor 1 (HBP-1), the target gene of miR-96, has been shown to inhibit Wnt/β-Catenin signaling pathway, and suppress cell proliferation and survival. Thus, miR-96 appears to promote tumor cell growth by down-regulation of HBP-1 in glioma cells [75]. Furthermore, the activation of β-Catenin/TCF/LEF-1 signaling pathway, which is stimulated by knock-down of glycogen synthase kinase 3 beta (GSK3β) [7], is known to induce up-regulation of miR-96 expression [7, 13]. As a serine/threonine protein kinase, GSK3β is essential for NF-κB-mediated anti-apoptotic response. Knock-down of GSK3β expression induces up-regulation of β-Catenin/TGF/LEF-1 complex, which binds to the promoter of miR-183-96-182 cluster and stimulates its transcription. Thus, up-regulation of the miR-183-96-182 cluster via GSK3β-mediated β-Catenin/TCF/LEF-1 signaling pathway can promote abnormal cell proliferation in gastric cancer [7]. The schematic diagram is provided in Appendix 1-2.

Previous studies have revealed that miR-183 and miR-182 promote cell proliferation, tumor invasion, and chemo-resistance by inhibition of programmed cell death 4 (PDCD4) in various cancer cells [55, 56, 76-81]. As a typical tumor suppressor gene (TSG), PDCD4 can inhibit eukaryotic translation initiation factor 4A1 (EIF4A1) and NF-κB-dependent transcriptional factors via direct interaction with p65, to induce apoptosis in glioblastoma cells [82]. The PDCD4-targeted inhibition by the miR-183-96-182 cluster, described in various cancers, is summarized in Table 1. Notably, miR-96 has also been found to inhibit the TSG RECK [40, 83, 84] and EFNA5 [85]. Besides, miR-96 and miR-182 were found to have an inhibitory effect on TP53INP1 expression [62, 86]. Collectively, the available evidence indicates that miR-183-96-182 cluster could promote cell proliferation in various cancer types (Table 1).
| Member of miR-183-96-182 cluster | Oncogene/ Tumor suppressor | Target genes | Tested in human cancer tissue | Cell lines | Cancer types | Results |
|--------------------------------|---------------------------|--------------|-------------------------------|------------|-------------|---------|
| miR-183-96-182 Oncogene       | FOXO1                     | --           | L428                          | Lymphoma  | Promotes cell proliferation [64] |
| miR-183-96-182 Oncogene       | FGF9, CPEB1, FOXO1        | ✓            | U251, U87                     | Glioma    | Promotes cell growth [65]       |
| miR-183-96-182 Oncogene       | RAB21(miR-183), RAB40B(miR-96 and miR-183), TNFSF11(miR-96) | ✓            | MCF-7, T47D                   | Breast cancer | Promotes cell proliferation [3] |
| miR-183-96-182 Oncogene       | --                        | ✓            | T24, UM-UC-3                 | Bladder Cancer | Promotes cell proliferation [154] |
| miR-183-96-182 Oncogene       | --                        | --           | R262, R300, UW402, UW426, D341, D384, D425, D458, D556, D283, DAOY | Medulloblastoma | Promote cell proliferation [155] |
| miR-96, miR-182 Oncogene      | FOXO1                     | ✓            | MCF-7, T47D, MDA-MB-231, MDA-MB-435 | Breast cancer | Promote cell proliferation [49] |
| miR-96, miR-182 Oncogene      | EFNA5                     | ✓            | HepG2, Hep3B, Huh7, SK-Hep1   | Hepatocellular carcinoma | Promote cell proliferation [85] |
| miR-96, miR-182 Tumor suppressor - | -                        | --           | A375, SK-MEL-28              | Melanoma | Inhibit cell proliferation [52] |
| miR-183 Oncogene              | PDCD4                     | ✓            | Eca109, TE13 and EC109, EC9706 | Esophageal cancer | Promote cell proliferation [76, 81] |
| miR-183 Oncogene              | PDCD4                     | ✓            | SGC-7901                     | Gastric cancer* | Promote cell proliferation [78] |
| miR-183 Oncogene              | NEFL                      | ✓            | U251                         | Glioma    | Promote cell proliferation [156] |
| miR-183 Oncogene              | PDCD4                     | ✓            | HepG2, Huh7                  | Hepatocellular carcinoma | Promote cell proliferation [79] |
| miR-183 Oncogene              | PDCD4                     | ✓            | SW1990                       | Pancreatic cancer | Promote cell proliferation [80] |
| miR-183 Oncogene              | SOCS-6                    | ✓            | PANC-1                       | Pancreatic cancer | Promote cell proliferation [157] |
| miR-183 Oncogene              | SOCS-6                    | ✓            | HepG2, Hep3B                 | Hepatocellular carcinoma | Promote cell proliferation [158] |
| miR-183 Oncogene              | PP2A-Cα, PP2A-Cβ, PP2A-B56-γ | ✓            | ACHN, A498                   | Renal cancer | Promote cell proliferation [104] |
| miR-183 Oncogene              | DKK-3, SMAD4               | ✓            | PC-3, DU-145, LNCaP          | Prostate cancer | Promote cell proliferation [159] |
| miR-183 | Tumor suppressor | BMI1 | Gastric cancer* | Inhibit cell proliferation [103]. |
|---------|------------------|------|----------------|--------------------------------|
| miR-96  | Oncogene         | FOXO1| Endometrial cancer. | Promote cell proliferation [70]. |
| miR-96  | Oncogene         | FOXO1| Hepatocellular carcinoma | Promote cell proliferation [160]. |
| miR-96  | Oncogene         | FOXO1| Bladder cancer | Promote cell proliferation [68]. |
| miR-96  | Oncogene         | FOXO1| PC3, LNCaP, and LNCaP, DU-145, PC3, 22rv-1, and 22Rv1, LNCaP clone FGC, DU145, PC3 | Promote cell proliferation [63, 66, 67]. |
| miR-96  | Oncogene         | FOXO1| SW480, SW620 | Promote cell proliferation [62]. |
| miR-96  | Oncogene         | FOXO3| Hepatocellular carcinoma | Promote cell proliferation [160]. |
| miR-96  | Oncogene         | FOXO3| SW480, SW620 | Promote cell proliferation [62]. |
| miR-96  | Oncogene         | FOXO3| MCF-7, ZR-75-30, BT549, Bcap37, MDA-MB435, SKBR3, MDA-MB453, T47D | Breast cancer | Promote cell proliferation [69]. |
| miR-96  | Oncogene         | FOXO3| A549, SPC-A-1 | Lung cancer*** | Promote cell proliferation [61]. |
| miR-96  | Oncogene         | RECK | MDA-MB-231, MCF-7, MDA-MB-468, MDA-MB-435, T-74D, MDA-MB-453 | Breast cancer | Promote cell proliferation [83]. |
| miR-96  | Oncogene         | RECK | A549, SK-MES-1, H1299 | Lung cancer*** | Promote cell proliferation [84]. |
| miR-96  | Oncogene         | HBP1 | U-87 MG, U-251 MG, U-373 MG, M059J | Glioma | Promote cell proliferation [75]. |
| miR-96  | Oncogene         | MTOR | LNCaP, 22Rv-1 | Prostate cancer | Promote cell proliferation (Under hypoxia) [23]. |
| miR-96  | Tumor suppressor | KRAS | HPDE , BxPC-3, PK-8, and MIA PaCa-2, PANC-1, BxPC-3 | Pancreatic cancer | Inhibit cell proliferation [20, 51]. |
| miR-96  | Tumor suppressor | HERG1 | PANC-1, SW1990, CFPAC-1, HPAC, BxPC-3 | Pancreatic cancer | Inhibit cell proliferation [89]. |
| miR-96  | Tumor suppressor | GPC1 | Panc-1, AsPC-1, BxPC-3 | Pancreatic cancer | Inhibit cell proliferation [90]. |
| miR-96  | Tumor suppressor | ALK | Karpos 299, SUP-M2, SU-DHLL-1, SR-786, DEL, SH-SY5Y, H2228 | Lymphoma, Neuroblastoma, and lung *** cancer | Inhibit cell proliferation [88]. |
| miR-96 | Tumor suppressor | ATG7 | ✓ | LNCaP, 22rv-1 | Prostate cancer** (Under hypoxia) [23]. |
| miR-96 | Tumor suppressor | REV1, RAD51 | -- | U2OS, HeLa, HCC1937, MDA-MB-231, HCT116, PEO1, PEO1 C4-2 | Multiple tumors | Sensitize cancer cells to cisplatin and PARP inhibition [36]. |
| miR-182 | Oncogene | PDCD4 | ✓ | A549, SPC-A-1 and A549 | Lung cancer**** Promote cell proliferation [55, 56]. |
| miR-182 | Oncogene | PDCD4 | -- | OVCAR3, SKOV3, OV2008, HEY, 3AO, A2780, HO8910, C13 | Ovarian cancer | Promote cell proliferation [77]. |
| miR-182 | Oncogene | CHL1 | ✓ | TPC-1, BCPAP | Papillary thyroid carcinoma | Promote cell proliferation [161]. |
| miR-182 | Oncogene | SATB2 | ✓ | DLD-1, HCT116, SW480, SW620, Lovo | Colorectal cancer | Promote cell proliferation [162]. |
| miR-182 | Oncogene | FOXF2 | ✓ | HT29, SW480, SW620, HCT116 | Colorectal cancer | Promote cell proliferation [71]. |
| miR-182 | Oncogene | CEBPA | ✓ | -- | Hepatocellular carcinoma | Promote cell proliferation [164]. |
| miR-182 | Oncogene | TP53INP1 | ✓ | HEK293, HepG2 | Hepatocellular carcinoma | Promote cell proliferation [86]. |
| miR-182 | Oncogene | LRRC4 | ✓ | U251, SF126, SF767 | Glioma | Promote cell proliferation [165]. |
| miR-182 | Oncogene | TCEAL7 | -- | HEC-1B, AN3CA, RL95-2, AN3CA | Endometrial carcinoma | Promote cell proliferation [166]. |
| miR-182 | Oncogene | CUL5 | ✓ | Ishikawa H | Endometrial carcinoma | Promote cell proliferation [167]. |
| miR-182 | Oncogene | NDRG1 | ✓ | LNCap, PC-3, DU145, 22Rv1 | Prostate cancer***** Promote cell proliferation [126]. |
| miR-182 | Oncogene | FOXF2, RECK, MTSS1 | ✓ | LNCap, PC-3, DU145 | Prostate cancer***** Promote cell proliferation [72]. |
| miR-182 | Oncogene | PFN1 | ✓ | MDA-MB-231 | Breast cancer | Promote cell proliferation [168]. |
| miR-182 | Oncogene | RECK, Smad4 | ✓ | J82, T24, UM-UC-3 | Bladder cancer | Promote cell proliferation [169]. |
| miR-182 | Oncogene | FOXO3 | -- | A549, H1299, CL 1-0, CL 1-5 | Lung cancer**** Promote cell proliferation [16]. |
Interestingly, in certain cancers, over-expression of miR-183-96-182 cluster had an inhibitory effect on cell proliferation, a finding which is not consistent with the earlier reports related to most cancer types. The miR-96 target gene, ATG7, is a key factor in the autophagy pathway, which protects the cancer cells against stress responses such as hypoxia or starvation [87]. High-expression of miR-96 is thought to inhibit autophagy through directly targeting ATG7, and subsequently inhibit the survival of cancer cells under hypoxic conditions [23]. In addition, miR-96 is known to down-regulate RAD51 (a DNA repair protein) and REV1 (a DNA polymerase) to promote cellular sensitivity to cisplatin, which binds to and cause crosslinking of DNA to ultimately trigger apoptosis [36]. Similar results were also found for miR-182 in acute myelogenous leukemia [21]. Thus, the over-expression of miR-96/miR-182 appears to dramatically promote drug sensitization in cancer cells [36]. miR-96 was also shown to inhibit cell proliferation of ALK-expressing cancer cells via suppressing ALK expression, as well as those ALK-targeted genes, including AKT, STAT3, JNK and IGF-1 [88].

Notably, the inhibitory effect of miR-96 on pancreatic cancer cell proliferation has been clearly elucidated in the past few years [20, 51, 89, 90]. In pancreatic cancer, three important oncogenes, including
### Table 2: miR-183-96-182 cluster in tumor invasion, migration, and metastasis.

| Member of miR-183-96-182 cluster | Oncogene/Tumor suppressor | Target genes | Cell lines | Cancer types | Results |
|----------------------------------|---------------------------|--------------|------------|--------------|---------|
| miR-183-96-182                   | Oncogene                 | RAB21(miR-183) RAB40B(miR-96 and miR-183) TNFSF11(miR-96) | MCF-7, T47D | Breast cancer* | Promote migration [3]. |
| miR-183-96-182                   | Oncogene                 | BRMS1L        | MCF-7, T47D, MDA-MB-435s, MDA-MB-468 | Breast cancer* | Promote EMT and invasion [15]. |
| miR-183-96-182                   | Oncogene                 | --            | R262, R300 UW402, UW426, D341, D384, D425, D458, D556, D283, DA0Y | Medulloblastoma | Promote migration [155]. |
| miR-183-96-182                   | Oncogene                 | FOXO1         | Hep3B, SNU387, HKCl-1, HKCl-8 | Hepatocellular carcinoma | Promote migration [13]. |
| miR-183-96-182                   | Tumor suppressor         | FOFOX2        | 55 human NSCLC cell lines | Lung cancer | Inhibit invasion and metastasis [116]. |
| miR-183, miR-96                  | Tumor suppressor         | SLUG, ZEB1, ITGB1, and KLF4 | HCT116, MCF10A | Colon cancer*** | Inhibit EMT, migration, and invasion [9]. |
| miR-96, miR-182                  | Oncogene                 | EFNA5         | HepG2, Hep3B, Huh7, SK-Hep1 | Hepatocellular carcinoma | Promote invasion [85]. |
| miR-183                          | Oncogene                 | --            | HTori-3, FTC-133 | Follicular thyroid carcinomas | Promote migration [171]. |
| miR-183                          | Oncogene                 | PDCD4         | Eca109, TE13 | Esophageal cancer | Promote invasion [76]. |
| miR-183                          | Oncogene                 | PDCD4         | SGC-7901 | Gastric cancer** | Promote invasion [78]. |
| miR-183                          | Oncogene                 | PDCD4         | SW1990 | Pancreatic cancer | Promote invasion and migration [80]. |
| miR-183                          | Oncogene                 | SOCS-6        | PANC-1 | Pancreatic cancer | Promote invasion and metastasis [157]. |
| miR-183                          | Oncogene                 | SOCS-6        | HepG2, Hep3B | Hepatocellular carcinoma | Promote invasion [158]. |
| miR-183                          | Oncogene                 | PP2A-Cα, PP2A-Cβ, and PP2A-B56-γ | ACHN, A498 | Renal cancer | Promote migration and invasion [104]. |
| miR-183                          | Oncogene                 | EGR1 and PTEN | SYO-1, FUJI, HCT116, DLD1, Rh30, JR1 | Synovial sarcoma, RMS, and colon*** cancer | Promote migration [105]. |
| miR-183                          | Oncogene                 | NEFL          | U251 | Glioma | Promote invasion [156]. |
| miR-183                          | Tumor suppressor         | TIAM1         | SKOV-3ip, HO-8910PM | Ovarian cancer | Inhibit migration and invasion [124]. |
| miR-183                          | Tumor suppressor         | BMI1          | AGS, SGC7901, MKN28, MGC803, HGC27 | Gastric cancer** | Inhibit invasion [103]. |
| miR-183                          | Tumor suppressor         | EZR           | MGC-803, SGC-7901, BGC-823, MKN-45, MKN-28 | Gastric cancer** | Inhibit invasion [120]. |
| miR-183                          | Tumor suppressor         | EZR           | SOSP-9607, and MG63, U2OS, Saos2, HOS, SV40 | Osteosarcoma | Inhibit migration and invasion [118, 119]. |
| miR-183                          | Tumor suppressor         | EZR           | MDA-MB-231, T47D, SKBR-3, ZR-75-1 | Breast cancer* | Inhibit migration [121]. |
| miR-183                          | Tumor suppressor         | EZR           | 801D, 95C | Lung cancer | Inhibit migration [122]. |
| miR-183 | Tumor suppressor | MMP-9 | Siha, HeLa | Cervical carcinoma | Inhibit invasion and metastasis [172]. |
| miR-183 | Tumor suppressor | ITGB1 and KIF2A | HeLa | Cervical carcinoma | Inhibit migration and invasion [125]. |
| miR-96 | Oncogene | RECK | MDA-MB-231, MCF-7, MDA-MB-468, MDA-MB-435, T-74D, MDA-MB-453 | Breast cancer | Promote invasion [83]. |
| miR-96 | Oncogene | MAP4K1 and IRS1 | T24 | Bladder cancer | Promote invasion [108]. |
| miR-96 | Oncogene | -- | AGS | Gastric cancer | Promote invasion [7]. |
| miR-96 | Oncogene | -- | HCCCLM6 | Hepatocellular carcinoma | Promote invasion [107]. |
| miR-96 | Oncogene | AKT1S1 | DU145, PC3, LNCap, 22Rv1, RasB1, AC1, AC3 | Prostate cancer | Promote bone metastasis [106]. |
| miR-96 | Tumor suppressor | KRAS | HPDE, BxPC-3, PK-8, and MIA PaCa-2, PANC-1, BxPC-3 | Pancreatic cancer | Inhibit migration and invasion [20, 51]. |
| miR-182 | Oncogene | MTSS1 | HLE, HepG2, Hep3B, HUH-1 | Hepatocellular carcinoma | Promote invasion [173]. |
| miR-182 | Oncogene | CYLD | LN382T, A172, T98G, LN18, LN229, LN464, SNB19, U373MG, U87MG, LN444, LN443, LN428, U118MG, LN-Z308, LN319 | Glioma | Promote invasion [8]. |
| miR-182 | Oncogene | RECK | MCF-7, MDA-MB-231, SKBR3, BT-20 | Breast cancer | Promote tumorigenicity and invasion [12]. |
| miR-182 | Oncogene | MIM | 4T1 series, MCF10 series | Breast cancer | Promote invasion and metastasis [174]. |
| miR-182 | Oncogene | PFN1 | DA0Y, D458 Med, Med8A | Medulloblastoma | Promote migration [175]. |
| miR-182 | Oncogene | -- | STS-48, STS-109, STS-145, primary mice sarcomas cell lines (Kras and p53 mutation) | Sarcomas | Promote migration, invasion and metastasis [176]. |
| miR-182 | Oncogene | RSU1, MTSS1, PAI1, and TIMP1 | Primary mice sarcomas cell lines | Sarcomas | Promote metastasis [18]. |
| miR-182 | Oncogene | CHL1 | TPC-1, BCPAP | Papillary thyroid carcinoma | Promote invasion [161]. |
| miR-182 | Oncogene | SATB2 | DLD-1, HCT116, SW480, SW620, Lovo | Colorectal cancer | Promote migration, invasion and metastasis [162]. |
| miR-182 | Oncogene | FOXF2 | HT29, SW480, SW620, HCT116 | Colorectal cancer | Promote invasion [71]. |
| miR-182 | Oncogene | TSP-1 | HCT-116, HT-29 | Colon cancer | Promote metastasis [177]. |
| miR-182 | Oncogene | PDCD4 | A549 | Lung cancer**** | Promote invasion [56]. |
| miR-182 | Oncogene | PDCD4 | OVCAR3, SKOV3, OV2008, HEY, 3AO, A2780, HO8910, C13 | Ovarian cancer | Promote invasion [77]. |
KRAS [51], human either a go-go-related gene type 1 (HERG1) [89] and Glypican 1 (GPC1) [90], are known to be miR-96 target genes. KRAS, aberrantly activated in approximately 90% of pancreatic cancers [91], can promote abnormal cell proliferation by activating PI3K/Akt, NF-κB and ERK signaling pathways [92-95]. HERG1 is over-expressed in various cancer cells and found to promote cell proliferation [96-98]. GPC1 is exhibited high-expression in pancreatic cancers for efficient proliferation and angiogenesis [99]. miR-96 is known to target these three genes and, thereby, significantly increase the apoptosis rate in pancreatic cancer cells. However, the biological functions of miR-183 and miR-182 in pancreatic cancer are still unclear [80, 100]. Similar inhibitory effects were also observed in renal cell carcinoma and melanoma [52, 101, 102]. In contrast to the usual oncogenic function of the miR-183-96-182 cluster in most cancer types, the above tumor suppressor activity suggests a specific context (hypoxia/chemotherapy), phenotype, or cancer cell-dependent regulation of the miR-183-96-182 cluster in tumorigenesis.

**Contradictory results**

However the functions of miR-183-96-182 cluster in lung and gastric cancer are yet to be confirmed (Table 1). In non-small cell lung cancer, miR-96 was shown to promote cell proliferation by targeting FOXO3 and RECK mRNA (A549, SK-MES-1, H1299 and SPC-A-1 cell lines) [61, 84], while according to a study by Vishwamitra et al., miR-96 inhibits cell proliferation by targeting ALK (H2228 cell line) [88]. This reported discrepancy in results may be attributable to the inclusion of different cell types for analysis or involvement of different signaling pathways. Two studies on gastric carcinoma simultaneously reported contradictory results with respect to the function of miR-183 during cell proliferation in SGC-7901 cells [78, 103], Xu et al. found miR-183 was down-regulated in 65 gastric cancer tissue and 5 gastric cancer cell lines, miR-183 significantly inhibited SGC7901 and AGS cell viability with MTT assay. In contrast, Gu et al. found miR-183 was up-regulated in 80 tumor tissue, miR-183 significantly promoted SGC7901 cell proliferation by MTT and flow cytometry assay. These
| Member of miR-183-96-182 cluster | Oncogene/ Tumor suppressor | Cancer types | Target genes | Results |
|--------------------------------|-----------------------------|--------------|--------------|---------|
| miR-183-96-182                 | Oncogene                    | Hepatocellular carcinoma (tissue) | FOXO1 | Associated with prognosis (microvascular invasion, tumor differentiation, and patients survival) [13]. |
| miR-183-96-182                 | Oncogene                    | Lung cancer (tissue and serum) | -- | Associated with prognosis (survival) [48]. |
| miR-183, miR-96                | Oncogene                    | Prostate cancer (tissue) | -- | Associated with prognosis (tumor aggressiveness, metastatic and overall survival) when combined with other microRNAs [131]. |
| miR-183                        | Oncogene                    | Lung cancer (tissue)* | -- | Associated with prognosis (lymph node metastasis, clinical stage and EGFR mutation and patients survival) [179]. |
| miR-183                        | Oncogene                    | Breast cancer (tissue) | -- | Associated with prognosis (TNM clinical stage) [129]. |
| miR-183                        | Oncogene                    | Colorectal cancer (plasma) | -- | Associated with cancer recurrence and prognosis (lymph node metastasis, distant metastasis, TNM stage) [132]. |
| miR-183                        | Oncogene                    | Colorectal cancer (tissue) | -- | Associated with prognosis (clinical stage, lymph node metastasis, distant metastasis and patients survival) [133]. |
| miR-183                        | Oncogene                    | Hepatocellular carcinoma (tissue) | -- | Associated with cancer progression (TNM stage and cirrhosis), but not with patient survival [130]. |
| miR-183                        | Oncogene                    | Hepatocellular carcinoma (serum) | -- | Associated with prognosis (TNM stage and postoperative survival) [180]. |
| miR-183                        | Tumor suppressor            | Lung cancer (serum) * | -- | Associated with prognosis (metastasis) [137]. |
| miR-183                        | Tumor suppressor            | Osteosarcoma (tissue) | EZR | Associated with aggressiveness and poor prognosis (tumor grade, response to chemotherapy, metastasis and recurrence) [135]. |
| miR-183                        | *                            | Prostate cancer (cancer cell) | KLK3/PSA | miR-183 binds to the 3' UTR of PSA and increases its protein and mRNA levels [136]. |
| miR-96                         | Oncogene                    | Prostate cancer (tissue) | -- | Associated with prognosis (tumor stage, recurrence and survival) [138]. |
| miR-96                         | Oncogene                    | Prostate cancer (tissue) | -- | Not correlates with prognosis (biochemical recurrence and clinicopathological parameters) [139]. |
| miR-96                         | Oncogene                    | Hepatocellular carcinoma (tissue) | LRP6, FOXO1A, and MAP2K1 (Not biologically validated) | Associated with prognosis (recurrence) when combined with other microRNAs [140]. |
| miR-96                         | Oncogene                    | Colorectal cancer (tissue) ** | -- | Associated with prognosis (overall survival) [32]. |
| miR-96                         | Tumor suppressor            | Colorectal cancer (plasma) ** | KRAS | Associated with prognosis (distant metastasis and survival) [181]. |
| miR-96                         | Oncogene                    | Acute myeloid leukemia (mononuclear cells) | -- | Associated with prognosis (relapse-free survival and overall survival) [141]. |
| miR-182                        | Oncogene                    | Nasopharyngeal carcinoma (tissue) | -- | Associated with prognosis (overall survival, disease-free survival, and distant metastasis) [144]. |
| miR-182                        | Oncogene                    | Pancreatic cancer (plasma) | -- | Associated with prognosis (Clinical stages, lymph node metastasis and survival) [143]. |
| miR-182                        | Oncogene                    | Breast cancer (tissue) | -- | Associated with prognosis (lymph node metastases and grade III occurrence) [142]. |
| miR-182                        | Oncogene                    | Colon cancer (tissue) | FBXW7 | Associated with prognosis (Survival) [145]. |
findings suggest that the regulation of cell proliferation by miR-183-96-182 cluster is a complicated synergic process, and the different functions of this cluster may be due to that the target genes might be expressed at different levels, contain mutations, or compete with other molecules. Other possible reasons for the contradictory results are summarized in Appendix 1-3.

### miR-183-96-182 cluster in tumor invasion and metastasis

**miR-183-96-182 cluster promotes tumor invasion and metastasis**

It has been demonstrated that miR-183-96-182 cluster promotes tumor invasion and metastasis in most cancers, including thyroid, esophagus, gallbladder, ovary, bladder, kidney, liver cancers, melanoma, medulloblastoma, sarcoma, glioma, and myeloid cell tumor (Table 2). miR-183 promotes tumor invasion and metastasis by targeting PDCD4, protein phosphatase 2A (PP2A), EGR1 and PTEN [76, 78, 104, 105]. In addition, TGF-β and Smad can also promote prostate cancer bone metastasis by induction of miR-96 and activation of the mTOR pathway [106]. Moreover, the inhibitory effect on metastasis in hepatoma carcinoma cells, induced by the suppression of miR-96 [107], was reported as being associated with the inhibition of EFNA5 expression by miR-96-targeting [85]. Similar findings have been reported in case of gastrin, bladder, and breast cancers [3, 7, 83, 108]. With regard to miR-182, Huynh et al. reported significant suppression of invasive growth tendency and metastasis by suppressing miR-182 in vivo [109]. Moreover, similar to the effects of TGF-β on miR-96, TGF-β up-regulates miR-182, which can target CYLD and thus promote the activation of NF-κB in glioblastoma. Therefore, TGF-β-mediated up-regulation of miR-182 probably results in the persistent activation of NF-κB in glioblastoma, which subsequently leads to angiogenesis and tumor invasion. Table 2 shows the target genes of miR-183-96-182 cluster which regulate invasion and metastasis in various tumor cells.

**miR-183-96-182 cluster inhibits tumor invasion and metastasis**

On the contrary, miR-183-96-182 suppresses tumor metastasis in lung, colon, and pancreatic cancers (Table 2). Transcriptional repressor Zinc C finger E-box-binding homeobox 1 (ZEB1) family is a series of transcription factors which contain zinc finger domain. The highly conserved zinc finger structure can bind to E-box domain of the promoter of target genes, such as E-cadherin, the key epithelial marker for epithelial-mesenchymal transition (EMT and MET) [110, 111]. A recent study indicated a ZEB1/miR-200 double negative feedback loop in EMT at different stages of tumor development [112]. Notably, miR-183/96 can inhibit EMT via suppressing ZEB1 expression. Besides, ZEB1 can also block the transcription of miR-183-96-182 cluster by binding to its promoter [9]. miR-183-96-182 cluster and ZEB1 exert a double negative feedback loop in p21-/- cells. However, more recently, p21, an inhibitor of cyclin-dependent kinase through suppressing the expressions of CDK1 and CDK1 proteins [113], can also inhibit EMT progression [114, 115]. There is further evidence that p21 can interact with ZEB1 to form a complex and binds to the promoter of miR-183-96-182 cluster, which suppresses the transcription inhibition by ZEB1 and results in the suppression of EMT. The schematic diagram is provided in Appendix 1-4. Similar results were also reported in lung cancer cells by Kundu et al., where they found that FOXF2 correlates with ZEB1 expression, and miR-183-96-182 can suppress FOXF2 to inhibit tumor invasion and metastasis in lung cancers [116].
The EZR gene, the target gene of miR-183, plays an important role in angiogenesis and tumor metastasis in various tumors [117]. The miR-183 was found to block MAPK/ERK signaling pathway, as well as inhibit tumor invasion and metastasis by suppressing EZR expression in gastric, breast, lung cancers, and osteosarcoma [118-122]. Additionally, several previous studies demonstrated that some oncogenes, including TIAM1, BMI1, TSP-1, FOXO3, GNA13, ITGB1, KIF2A, SLUG, ITGB1, and KLK4, were targeted by miR-183 and miR-96 for the suppression of invasion and metastasis in oophoroma, lung, prostate, colon, cervix, stomach and pancreas cancer cells [9, 16, 20, 51, 103, 123-125] (Table 2).

**Contradictory results**

Investigations of the effects of miR-183-96-182 cluster on tumor invasion and metastasis have sometimes yielded contradictory results in different tumors, and in some cases, even within the same tumor type. miR-183 was found to be down-regulated by Caos et al. (in 52 pairs of FFPE samples and 5 cell lines) and Xus et al. (in 65 pairs of samples and 5 cell lines) (Table 2) and hypothesized to inhibit tumor invasion by suppressing the expressions of BMI1 or EZR proteins in gastric cancers [103, 120]. Conversely, Hues et al. reported that miR-183 was up-regulated (20 non-tumor tissue and 80 tumor tissue samples) and promotes gastric cancer cell invasion by inhibiting PDCD4 expression [78]. Similar differences in results were also reported in case of prostate cancers. miR-182 was over-expressed in prostate cancer tissue by Hirata et al. (52 paired samples) and Liu et al. (5 tumor and 3 non-tumor tissue) and enhanced the invasive and migratory capacity in PC3 and DU145 cells by targeting NDRG1, FOXF2, RECK, and MTSS1 genes [72, 126]. In contrast, over-expression of miR-182 was shown to inhibit tumor invasion in PC3 and LNCaP cells by suppressing GNA13 expression [123]. These findings suggest a context-dependent phenotype for the miR-183-96-182 cluster in carcinogenesis which needs to be further investigated to understand the complex interactions, especially in those cancers where contradictory results have been observed, such as prostate, colon, lung, breast, and gastric cancers (Table 2).

**miR-183-96-182 cluster in cancer prognosis**

Most of cancer cells display high-expression of miR-183 [127, 128]. The up-regulation of miR-183 is known to be associated with poor prognosis in breast cancer, colorectal cancer, hepatocellular cancer, and prostate cancer [13, 129-134], while predicts a good prognosis in osteosarcoma [135] (Table 3). This finding is consistent with its functions in cell proliferation, invasion and metastasis in these tumors types. Notably, miR-183 might affect the prediction for PSA-dependent diagnosis and prognosis via regulating PSA expression [136]. With respect to the prediction of miR-183-related prognosis, the available evidence from different studies is contradictory in lung cancer. Lin et al. showed the low expression of miR-183 in the peripheral blood which was associated with increased TNM stage in lung cancer patients (13 squamous-cell carcinoma and 17 adenocarcinoma) [137]. While Zhu et al. demonstrated the up-regulation of miR-183 family in lung cancer tissue (36 squamous-cell carcinoma and 34 adenocarcinoma), and that it appeared to confer a poor prognosis [48]. The wide variability in the reported results may be attributable to the differences between blood and tissue or the heterogeneity in lung cancer cells.

The high expression of miR-96 in prostate cancer is well documented [23, 41, 63, 66, 67, 138]. Larnes et al. recently reported a miRNA index quote (miQ) in prostate cancer, which uses four miRNAs (miR-96, 183, 145, and 221) for more accurate diagnosis (area under the curve, AUC = 0.931) and prognosis (AUC = 0.895 for predicting aggressiveness and AUC = 0.827 for metastasis). miQ was verified in an independent Dutch cohort and three external cohorts, and significantly outperformed the prostate-specific antigen [131]. Schaefer et al. demonstrated that highly expressed miR-96 can predict cancer recurrence after radical prostatectomy [138]. Additionally, Haflidadottir et al. found miR-96 expression correlated with WHO grade, and the overall survival time in prostate cancer [67]. In contrast, a recent investigation found no significant correlation between the expression of miR-96 and clinicopathological parameters [139]. Thus, suggesting that more studies are required to understand the prognostic relevance of miR-96. In addition, miR-96 was reported as a potential biomarker for the predicting recurrence after surgical resection of hepatocellular cancer [140], and as prognostic indicator in lung cancer, colorectal cancer and acute myeloid leukemia [32, 48, 141] (Table 3).

Corresponding to the biological functions of miR-182 in various tumors, the up-regulation of miR-182 was associated with poor prognoses in hepatocellular carcinoma [13], breast cancer [142], pancreatic cancer [143], oropharyngeal carcinoma [144], colorectal adenocarcinoma [145-148], prostate cancer [149], bladder cancer [150], and glioblastoma [151] (Table 3). In contrast, the up-regulation of miR-182 was found to correlate with good prognosis in lung cancer [152]. We presume that this might be associated with the miR-183 target genes, such as RGS17, RASA1, CTTN, and FOXO3, which have been shown to inhibit cell proliferation, tumor invasion and metastasis in lung cancer cells [16, 57, 58, 153].

**CONCLUDING REMARKS**

Recent studies suggest an important role of miR-183-96-182 cluster in tumorigenesis, cancer progression, tumor invasion and metastasis. Although
most of the reports showed that miR-183-96-182 cluster is an oncogene cluster, it also functions as a TSG by inhibiting cell proliferation and metastasis in certain cancer cells. We hypothesize that the different results observed in expression and function of the miR-183-96-182 cluster may result from different underlying tissue types, different expression abundance of miR-183-96-182 or their target genes, differences between cell lines (Table 1-2), differences between cell line and tumor tissue, tissue and blood (Table 3), and differences between detecting methods used. Recent studies have also indicated diagnostic and prognostic relevance of the members of miR-183-96-182 cluster, either independently or collectively. These new data on the functions of miR-183-96-182 cluster in various tumors suggest that further studies will be needed to clarify its functions in the various stages and histological subtypes in different types of tumors, which will significantly improve the accuracy of the prediction for tumor diagnosis or prognosis. As regards the conflicting results in certain tumors, we believe that miR-183-96-182 cluster might play different roles because of tumor heterogeneity, which will be important for the individual diagnosis and prognosis in anti-tumor treatment.

Abbreviations

miRNA, microRNA; TSS, transcriptional start site; TSG, tumor suppressor gene; EMT, epithelial-mesenchymal transition.

CONFLICTS OF INTEREST

The authors disclose no potential conflicts of interest.

GRANT SUPPORT

This work was supported by the National Natural Science Foundation of China (Grant No.81501310, 81571499, 81370762, 81572536) and Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University (RJZZ14-009). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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