Down-regulated MicroRNAs in Gastric Carcinoma May Be Targets for Therapeutic Intervention and Replacement Therapy

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Abstract. Gastric cancer is one of the leading types of cancer with an annual death toll of 700,000 worldwide. Despite the fact that several agents are approved for its treatment, high percentage of recurrence and intractability of metastatic disease remain a major problem. The identification of new targets and modalities for treatment are therefore of high priority. We have searched the literature for microRNAs down-regulated in gastric cancer with efficacy in gastric cancer-related murine xenograft models after reconstitution therapy. Among the identified miRs were 25 miRs targeting transcription factors, seven of them regulating cell-cycle and apoptosis-related targets, and five of them regulating GTPase-related targets such as GAPs and GEFs. According to criteria such as prognostic impact, functional data, and tractability, miR-133 b/a (*MCL1*) and miR-518 (*MDM2*) are suggested as potentially valuable targets for further evaluation and possible treatment of gastric cancer.

Gastric cancer (GC) is the third-leading cause of cancer worldwide and is the fourth most common cancer with an annual worldwide death toll of 700,000 (1). Stomach tumor types include esophageal gastric cancer, gastrointestinal stromal tumors (GIST) and gastric cancer (GC) (1). In this review we focus on gastric cancer (GC). From a histopathological point of view intestinal and diffuse subtypes

of GC have been identified. The first is characterised by well differentiated tubular and glandular structures, and the second by undifferentiated or poorly differentiated cells and lack of gland formation (1). From a molecular point of view the following subtypes have been characterized: Epstein-Barr-Virus (EBV), microsatellite instability (MSI), genomically stable (GS) and chromosomal instability (CIN) subtypes, all correlated with differential prognosis (2). The standard therapy of GC patients is platinum- and fluoropyrimidine-based chemoradiotherapy or patient subgroup-specific therapy with Herceptin and chemotherapy or the vascular-endothelial growth factor receptor 2 (VEGFR2) monoclonal antibody (mAb) Ramucirumab in combination with other agents (3, 4). Several Phase III studies are ongoing with immune checkpoint-related mAbs directed against cytotoxic T-lymphocyte associated protein 4 (CTLA4), programmed death 1 (PD1) and programmed death-ligand 1 PD-L1 (3, 4). So far, surgery is the only potentially curative therapy, yet still more than half of radically resected GC patients relapse locally or develop distant metastasis (3, 4). Preferential organs of metastasis are the liver (48%), peritoneum (32%), lung (15%) and bone (12%) (5). Relapsed and metastatic GC only poorly respond to established treatment regimens (3, 4). Regarding the molecular genetics of GC, mutations or loss of heterozygosity of adenomatous-polyposis-coli (APC) (6), chromatin-remodelling protein AT-rich interactive domain containing protein 1A (ARID1A) (7, 8), cell adhesion protein E-cadherin (9) and Ras homolog family member A (RHOA) involved in regulation of the cytoskeleton have been identified (10, 11). Altogether, the identification of new targets and treatment modalities for GC is highly desired. In this review, we describe the role of miRs that are down-regulated in GC, representing tumor-suppressive microRNAs (miRs) affecting transcription factors, cell-cycle related and anti-apoptotic proteins as well as miRs that affect small GTPases and their interacting proteins and proteins such as

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guanine nucleotide exchange factors (GEFs) and GTPases activating proteins (GAPs), in pathogenesis and metastasis of GC. We focus on miRs which are down-regulated in GC tissue in comparison to corresponding normal tissues and exhibit efficacy in preclinical *in vivo* models.

Roles of microRNAs in Oncology

microRNAs (miRs) are double-stranded RNAs comprising 22-25 nts and are generated from hairpin-containing precursor transcripts (12). They are transcribed in the nucleus by RNA polymerase II, processed, exported to the cytoplasm and released as 22-25 nts miR-duplexes (13, 14). One of the strands of the RNA duplex is maintained (guide strand), the other strand (passenger strand) is degraded (13, 14). Subsequently, the guide strand binds to the 3'-untranslated region (3'-UTR) of the mRNA of the corresponding targets and mediates their degradation and/or inhibition of their translation (13, 14). In contrast to interfering RNA (RNAi) which targets a single type of mRNA, miRs can affect up to several hundreds of different mRNAs (15). Therefore, miRs can modulate several oncogenic and tumor-suppressive pathways and hence have the potential of rewiring tumor cells to a differentiated state (15). In humans, approximately 1,000 genes encoding miRs have been identified so far (16). They are positioned as separate or clustered genes, in introns or in coding regions (6). miRs can act as oncogenes as well as tumor suppressors (16). Their actual function can be context-dependent (16).

In a proof-of-concept experiment (POC) it was shown that expression of the miR-15/16 cluster in mice prevents chronic lymphocytic leukemia analogous to the human disease by targeting B cell lymphoma 2 (BCL2) (17). In another POC experiment an oncogenic role was identified for miR-221, which induced hepatocellular carcinoma in transgenic mice after liver-specific expression (18). miRs play a role in tumorigenesis, angiogenesis, tumor-stromal interactions, and metastasis (19). We have recently summarized their role in metastasis in breast, prostate, ovarian, lung, pancreatic and liver cancer (20-25).

miRs Targeting Transcription Factors

miR-15a-3p and miR-16-1-3p target TWIST-1. Over-expression of miRs -15a-3p and -16-1-3p (Figure 1A) in BGC-823 GC cells suppresses migration, invasion and colony formation *in vitro* (26). Twist family basic helix-loop-helix (BHLH) transcription factor 1 (TWIST-1), which is involved in the epithelial mesenchymal transition (EMT) process by up-regulation of N-Cadherin and down-regulation of E-Cadherin and is over-expressed in GC, has been shown to be a direct target of both miRs (26-28). TWIST-1 over-expression induced cell migration and invasion (26). Both miRs suppress tumorigenicity in nude mice, whereas over-

expression of TWIST-1 reverses miR-mediated inhibition of tumorigenesis (26). In GC clinical samples, an inverse correlation between expression of miR-15a-3p, miR-16-1-3p and TWIST-1 mRNA and protein has been noted.

miR-141 and -200a,b,c target ZEB1,2. miRs -141 and -200c (Figure 1A) reduce invasion ability of the metastatic GC cell line 58As9 (29). In nude mice, synthetic mimics for miR-141 and -200c complexed with atelocollagen inhibit peritoneal dissemination to the omentum of orthotopically implanted 58As9 cells (29). miR-141 targets the transcription factor zinc finger E-box binding homeobox 2 (ZEB2), whereas miR-200c directly targets zinc finger E-box binding homeobox 1 (ZEB1) (29). Over-expression of miR-200a in SGC-7901 GC cells inhibits cell growth and invasion and induces G0/G1 phase arrest *in vitro* (30, 31). Transfection of miR-200a into SGC-7901 cells inhibits tumor growth (TG) *in vivo* in nude mice by up-regulation of E-cadherin and inhibition of WNT/ β -catenin signaling (30, 31). miR-200a inhibits EMT and targets ZEB1 and ZEB2 (30, 31). miR-200b over-expression in the GC cell lines MGC-803 and SGC-7901 induces an epithelial phenotype and suppresses TG in nude mice (32). miR-200b suppresses N-Cadherin, vimentin and ZEB1 and induces E-Cadherin *in vivo* (32). ZEB1 and ZEB2 are inducers of EMT and metastasis (33, 34). In GC patients, ZEB1 and ZEB2 expression is associated with poor survival (35).

miRs -105, -138 target SOX9 and SOX4. miRs-105 and -138 (Figure 1A) target sex determining region Y-related high mobility group 9 and 4 (SOX9 and SOX4) (36-38). Reduced levels of miR-105 and/or increased SOX9 expression are associated with poor survival in GC patients (36-38). miR-138 is reduced in GC patients with lymph node metastasis in comparison to patients without lymph node metastasis (38). miR-105 and -138 suppress proliferation, colony formation, migration, invasion and EMT of BGC-823 and SGC-7901 GC cells (36-38). Ectopically expressed miR-105 inhibits TG of SGC-7901 cells subcutaneously implanted into nude mice and their metastasis to the lungs (36, 37). miR-138 transfected SGC-7901 cells show decreased TG in nude mice after subcutaneous implantation (38). SOX proteins are transcription factors of a gene family of 20 members in humans, which bind to the minor groove of DNA by their high motility group (HMG) domain. They have a regulatory function in development, cell-fate decision, sex determination and differentiation (39, 40). Their deregulation leads to cancer initiation, progression and metastasis, angiogenesis and lymphatic angiogenesis and changes in the tumor microenvironment (39, 40). SOX4 expression has been associated with an unfavorable prognosis in GC patients (41). Expression of SOX9 correlates with poor clinical outcome in the MSS/TP53+ subgroup of GC patients (42).

Figure 1. Tumor-suppressive miRs targeting transcription factors and coactivators with activity in preclinical *in vivo* models. A: miRs targeting transcription factors: miRs-15a-3p, -16-1-3p, -141, -200c, -105, -138, -136, -489. HOXC10: Homeobox transcription factor C10; MAPK: mitogen activated protein kinase; NFκB: nuclear factor κB; PROX1: prospero homeobox protein 1; SOX 4,9: SRY-related HMG-box 4,9; TGFβ: transforming growth factor β; TWIST1: transcription factor TWIST1; WNT: WNT signaling; ZEB1,2: zinc finger E-box binding homeobox 1,2. B: miRs targeting further transcription factors: miRs- 27, -31, miR-33b, -494, -34, -145, -186, -320, -508-3p, -520b, -1297. c-MYC: Transcription factor c-MYC; COUP-TF2: chicken ovalbumin upstream promoter; CREB1: cAMP response element binding protein 1; E2F2: transcription factor E2F2; ETS1: E26 transformation specific-1; FOXM1: forkhead protein M1; HIF-1α: hypoxia-inducible factor 1; NFκB1: nuclear factor κB1; NR2F2: nuclear receptor 2 subfamily 2; HK2: hexokinase 2; PD-1L: programmed cell death ligand 1; PFKP: platelet isoform phosphofructokinase; p27-Kip1: cyclin-dependent kinase inhibitor1; YY1: Ying and Yang 1. C: miRs targeting transcriptional co-activators: miRs- 15a, -16-1, -141, -19b, -409-3p. BCL3: B-cell lymphoma 3; ERK: extracellular signal-regulated kinase; MEK: mitogen-activated protein kinase kinase, NFκB: nuclear factor κB; PHD10: PHD finger protein 10; TAZ: transcriptional co-activator with PDZ-binding motif; YAP: yes activated protein.

miRs-136 and -489 target homeobox genes *HOXC10* and *PROX-1*. miR-136 (Figure 1A) is down-regulated in GC peritoneal metastasis tissue and is associated with worse prognosis (43). GC-9811P GC cells expressing exogenous miR-136 display unaltered proliferation or apoptotic rates but show reduced mobility and invasion. *In vivo*, a decrease in peritoneal metastasis formation was noted in a murine tumor model (43). Homeobox protein HOXC10 was identified as a direct target of miR-136 (43). Knockdown of HOXC10 reduces migration and invasion of GC-9811P cells *in vitro* and abolishes metastasis in peritoneal colonization assays (43).

HOXC10 is a member of the human HOX gene family comprising 39 genes, which contain a homeobox gene sequence in the range of 180 bp with DNA binding capacity of the corresponding protein moiety (44). Homeobox genes

and their proteins regulate patterns of anatomical development in animals and humans. HOXC10 promotes cell proliferation and migration of GC cells through nuclear factor kappaB (NFκB), mitogen-activated protein kinase (MAPK) pathways and up-regulation of pro-inflammatory cytokines such as tumor necrosis factor α and β (TNFα,β), interleukin 6 (IL6) and epidermal growth factor (EGF) (45-48). miR-489 (Figure 1A) expression is reduced in GC tissues in comparison to corresponding normal tissues (49). miR-489 inhibits proliferation of AGS GC cells and tumorigenicity of AGS cells in nude mice after subcutaneous implantation (49). Prospero homeobox protein 1 (PROX-1) was identified as a direct target of miR-489 (49). Expression of PROX-1 is associated with progression and prognosis in GC (49). PROX-1 is a mediator of tumor cell proliferation,

angiogenesis and lymphangiogenesis and has been identified as a marker for lymphocytic endothelium (50, 51).

miR-27b targets NR2F2. miR-27b (Figure 1B) inhibits proliferation, migration, and invasion of MGC-803 GC cells (52). TG and metastasis to the liver of MGC-803 cells expressing exogenous miR-27b are inhibited after implantation into the stomach or the spleen of nude mice (52). Nuclear receptor subfamily 2, group F, member 2 (NR2F2), also referred to as chicken ovalbumin upstream promoter transcription factor-II (COUP-II) has been identified as a direct target of miR-27b (52). NR2F2 is an orphan nuclear receptor with a DNA and ligand binding domain and context-dependent oncogenic and tumor suppressive functions (53, 54). NR2F2 has crucial functions in cell differentiation and cell metabolism (53, 54). In GC, NR2F2 has been found to activate embryonic pathways through up-regulation of expression of Cadherins 6 to 11 (55). However, in GC also a tumor-suppressive function has been reported for NR2F2 through inhibition of proliferation, invasion, and metastasis (56).

miR-31 targets E2F2. miR-31 (Figure 1B) is down-regulated in GC and GC-derived cell lines in comparison to adjacent normal tissues and GES-1 cells (57). miR-31 over-expression in SGC-7901 and MGC-803 cells leads to cell-cycle arrest in the G1 phase, increase in apoptotic index and inhibition of migration and invasion (57). miR-31-mimic transduced SGC-7901 cells exhibit decreased TG after subcutaneous implantation into nude mice and decreased liver metastasis after tail vein injection (57). Transcription factor E2F2 has been identified as a direct target of miR-31 (57). Knock-down of E2F2 reduces cell migration and invasion of SGC-7901 and MGC-803 cells (57). E2F2 binds to retinoblastoma protein (Rb) and after its dissociation it can act as a transcriptional activator or repressor (58). However, the data for the role of E2F2 in GC cancer are controversial since increased expression of E2F2 also was associated with a favorable prognosis (59).

miRs-33b and -494 target c-MYC. miR-33b (Figure 1B) is down-regulated due to DNA methylation in GC samples in comparison to adjacent normal tissues. Its decrease correlates with disease progression and GC patients with metastases have lower levels of miR-33b than those without metastases (60). Over-expression of miR-33b inhibits proliferation, migration, and invasion of the GC cell lines MGC-803 and HGC-27 (60). Tumorigenicity of subcutaneously implanted HGC-27 cells in nude mice is suppressed following their transduction with miR-33b (60). The transcription factor c-MYC was identified as a target of miR-33b (60). miR-494 (Figure 1B) is down-regulated in GC samples and cell lines and is negatively correlated with survival (61). GC-derived

AGS cells that are transfected with miR-494 exhibit delayed G1/S entry (61). c-MYC was identified as a direct target of miR-494 (61). Tumor burden of subcutaneously implanted AGS cells into nude mice was attenuated by intraperitoneal injection of a miR-494 mimic (61). c-MYC is a transcription factor with basic helix-loop-helix and leucine zipper structural motifs, which activates many proliferative genes (62). In addition, c-MYC has an impact on cell growth, ribosomal RNA processing and other crucial physiological processes (63-66). c-MYC has been found to be deregulated in GC (67).

miR-34 targets YY1. Ying and Yang1 (YY1), a member of the GLI-Kruppel class of zinc finger transcription factors, was identified as the target of miR-34 (Figure 1B) family, which consists of miRs-34a, -b and -c (68). YY1 contributes to tumor sphere formation in GC-derived SC-M1 cells and up-regulates pluripotency genes cluster of differentiation 44 (CD44), octamer-binding transcription factor 4 (OCT4), SOX2 and homeobox protein NANOG. It is also involved in maintenance of the cancer stem cell (CSC) phenotype (68). Knock-down of YY1 in SC-M1 cells leads to expression of epithelial markers E-Cadherin and plakoglobin (a catenin protein family member homologous to β -catenin), and to decrease of mesenchymal markers N-Cadherin and vimentin (68). Transfection of SC-M1 cells with miR-34b and 34c inhibits tumor growth after subcutaneous implantation and lung metastases after tail vein injection in nude mice (68). miR-34a inhibitors expressed in SC-M1 cells lead to increased lung metastasis in the experimental metastasis assay system in nude mice (68). YY1 activates and represses many genes involved in cellular differentiation, DNA repair, cell division, survival, apoptosis, and autophagy with a context-dependent function as a tumor driver or suppressor (69, 70). YY1 expression contributes to gastric carcinogenesis and its nuclear expression correlates with survival in patients with early-stage gastric adenocarcinoma (71). YY1 also is involved in the regulation of cancer immune cell resistance by up-regulating PD-L1 (72).

miR-145 targets ETS-1. Transcription factor E26 transformation specific-1 (ETS-1) has been identified as a target of miR-145 (Figure 1B) (73). ETS-1 is the cellular homolog of the v-ETS oncogene, and is highly expressed in GC tissues and cell lines. Its expression inversely correlates with miR-145 levels (73). In SGC-7901 and MKN-45 GC cell lines, ectopic expression of miR-145 has no influence on proliferation, but inhibits migration, invasion, and tube formation (73). Transfection of ETS-1 restored the decrease in migration, invasion, and angiogenesis in SGC-7901 and MKN-45 cells mediated by miR-145 (73), whereas knockdown of miR-145 promoted migration, invasion, and angiogenesis (73). Knockdown of ETS-1 phenocopies the effects of miR-145 over-expression in GC cells *in vitro* (73). Transfection of SGC-

7901 cells with miR-145 has no influence on TG *in vivo*, but decreases lung metastasis after tail vein injection (73). The ETS family of transcription factors is composed of 28 members in humans and regulates genes involved in extracellular matrix (ECM) remodelling, migration, and invasion (74). ETS-1 induces genes such as matrix metalloproteinases 1 and 9 (MMP-1, -9) and urokinase plasminogen activator (uPA) (75) and is involved in EMT and angiogenesis (76). GC patients with tumors that express ETS-1 have poorer prognosis than those without expression of ETS-1 (77).

miR-186 targets HIF-1 α . miR-186 (Figure 1B) is down-regulated in GC (78). In MKN45 and SGC-7901 cells, miR-186 inhibits cell migration and proliferation and promotes apoptosis (78). Hypoxia-inducible factor-1 α (HIF-1 α) was identified as a direct target of miR-186 (78). miR-186 promotes down-regulation of hexokinase 2 (HK2) and platelet-type phosphofructokinase (PFKP), two enzymes involved in glycolysis (78). *In vivo* studies in nude mice with MKN45 and SGC-7901 cells support a tumor-suppressive role of miR-186 (78). Strongest growth inhibition was achieved by combination of miR-186 mimics and small hairpin (sh) HIF-1 α (78). In GC, HIF-1 α has an impact on apoptosis, EMT, and drug resistance (79, 80). HIF-1 α expression indicates a poor prognosis in GC patients (81, 82).

miR-320 targets FOXM1. Human GC exhibits low expression of miR-320 (Figure 1B) (83). Forkhead box protein M1 (FOXM1) was identified as a target of miR-320 (83). Over-expression of miR-320 in the GC cell lines AGS, BGC-823 and HGC-27 leads to inhibition of FOXM1 expression and up-regulation of cyclin-dependent kinase inhibitor 1B (p27KIP1) (83). Conversely, suppression of miR-320 in BGC-823 GC cells leads to increased TG in nude mice through altered FOXM1-p27KIP1 signaling (83). FOXM1 is frequently over-expressed in various cancers, functions as a proto-oncogene and plays a role in cell-cycle progression (84, 85). In GC, FOXM1 facilitates cell migration by inducing cathepsin (86) and cooperates with urokinase plasminogen activator (uPA) to promote disease progression (87). Expression of FOXM1 is associated with poor survival in patients with GC (88).

miR-508-3p targets NF κ B1. NF κ B1 (p50) and RelA (p65) are up-regulated in primary GC tumors as well as in GC-derived cell lines (89). NF κ B1 has been identified as a direct target of miR-508-3p in GC (89). NF κ B1 and transcription factor p65 (RELA) mediate proliferation, invasion, and colony formation of MKN28, MGC-803 and SGC-7901 GC cells (89). NF κ B1 expression shows a negative correlation with miR-508-3p (Figure 1B) expression in GC specimens (89). NF κ B1 expression counteracts the tumor-suppressive effect of miR-508-3p (89). *In vivo*, MGC-803 cells treated with

small interfering RNA (si) NF κ B1 grow slower than the untreated cell line after subcutaneous implantation into nude mice (89). In GC, NF κ B1 induces cytokines/chemokines, growth factors, anti-apoptotic factors, regulators of angiogenesis and metalloproteinases (90). Furthermore, it has been shown that signal transducer and activator of transcription (STAT3) and NF κ B cooperate to promote progression of GC (91).

miR-520b, -1297 target CREB1. miR-520b (Figure 1B) inhibits migration and invasion of GC cells BGC-823 and MKN45 (92). Expression of miR-520b is dependent on zinc transcription factor GATA-binding factor 6 (GATA6) (93), which in turn is down-regulated in metastatic GC specimens and GC-derived cell lines (92). Down-regulation of GATA6 correlates with poor prognosis in GC (92). cAMP response element binding protein 1 (CREB1) has been identified as a direct target of miR-520b. Ectopic expression of miR-520b inhibits migration and invasion of GC cell lines BGC-823 and MKN45 *in vitro* and *in vivo* in nude mice (93). miR-1297 (Figure 1B) also targets CREB1 and shows significantly lower expression in GC tissue samples compared to adjacent normal tissue (94). Lower expression of miR-1297 correlates with larger tumor size, lymph node metastases, advanced tumor/lymph node/metastasis (TNM) type and poor survival of GC patients (94). Conversely, up-regulation of miR-1297 leads to inhibition of proliferation and colony formation *in vitro* in GC cell lines and to suppression of TG in nude mice after subcutaneous implantation (94). Increased CREB1 expression rescued the *in vitro* effects of miR-1297 in GC cell lines. Independently, it has been shown that CREB1 promotes GC cell proliferation, colony formation, invasion and migration, and TG *in vivo* (95). CREB1 knock-down in GC cells leads to inhibition of cyclin D1 (CCND1), BCL2 and MMP9 (95). High expression of CREB1 is associated with increased tumor stage, metastasis, and poor outcome in GC patients (96).

Co-activators

miRs-15a, -16-1, -141 target YAP and TAZ. miR-15a and -16-1 (Figure 1C) are down-regulated in GC. In the cell lines AGS, MKN1 and MGC-803, ectopic expression of miRs-15a and -16-1 inhibits proliferation, migration as well as invasion, and induces G0/G1 cell-cycle arrest (97). Yes-associated protein 1 (YAP1) was identified as a direct target of miRs-15a and -16-1 (97). YAP1 re-expression abolishes in part the *in vitro* effects of miRs-15a and -16-1 (97). YAP1 activates the rapidly accelerated fibrosarcoma (RAF)/dual specificity mitogen-activated kinase kinase (MEK)/extracellular regulated kinase (ERK) pathway in GC cells (97). Reduced tumor sizes (*vs.* controls) were observed after transplantation of siYAP1 expressing MGC-903 cells in nude mice (97). miR-141 (Figure 1C) is down-regulated in primary GC-specimens and correlates

inversely with metastatic propensity of GC (98). miR-141 inhibits proliferation, invasion, and migration of GC cell lines BGC-823, HGC-27 and SGC-7901 by targeting transcriptional co-activator with PDZ-binding motif (TAZ) (98). HGC-27 GC cells transfected with a miR-141mimic show reduced TG after subcutaneous implantation into nude mice and decreased lung metastases after tail vein injection (98). YAP1 and its paralogue TAZ exert oncogenic activities after association with TEA-domain family (TEAD) transcription factors (99, 100). YAP1 and TAZ are repressed by Hippo pathway upstream regulators and are drivers of TG, metastasis, and resistance to therapy (101). It has been shown that YAP/TAZ initiates gastric tumorigenesis by c-MYC (102), and increased expression of TAZ is associated with EMT (103). Expression of TAZ in association with WNT pathway mutations impacts survival outcomes in advanced GC patients treated with first-line chemotherapy (104). YAP1 expression correlates with poor prognosis in GC patients (105).

miR-19b targets BCL3. miR-19b (Figure 1C) is down-regulated in GC tissues and cell lines and is associated with clinico-pathological factors and poor prognosis in patients (106). miR-19b inhibits cell proliferation and cell-cycle progression of GC cell lines MGC-803 and SGC-7901 (106). B-cell lymphoma 3 (BCL3) was identified as the target of miR-19b (106). Over-expression of miR-19b inhibits TG of MGC-803 GC cells subcutaneously implanted in nude mice (106). Also, silencing of BCL3 abolishes the effects of miR-19b inhibition on cell proliferation and cell-cycle progression (106). BCL3 acts as an oncogene in haematologic malignancies such as B-cell chronic lymphocytic leukemias. But it is also deregulated in solid tumors, modulating proliferation and cell death (107). BCL3 regulates transcription by forming complexes with p50 or p52 homodimers of the NFkB signaling pathway, and also by association with other transcription factors (108). However, the role of BCL3 in GC remains to be explored in more detail.

miR-409-3p targets PHD10. miR-409-3p (Figure 1C) is down-regulated in GC cell lines and tumors (109). In SGC-7901 cells, over-expression of miR-409-3p suppresses proliferation and induces apoptosis *in vitro* and *in vivo* in nude mice (109). PHD finger protein 10 (PHD10) was identified as a target of miR-409-3p (109). Expression of the human PHD10 (plant homeodomain containing gene 10) is required for cell proliferation in normal and SV40 immortalized human fibroblasts (110). In GC, PHD10 exerts an anti-apoptotic function by suppressing caspase 3 (111).

Cell-cycle and Apoptosis

miR-29c targets CCND2. miR-29 (Figure 2) is a family consisting of three members (29a-, b- and c) with miR-29c

Figure 2. Tumor-suppressive miRs targeting cell-cycle related and anti-apoptotic mRNAs with activity in preclinical *in vivo* models: miRs-29c, -12b, -133b/a, -137, -181d, 376-3p, -518, -1254. BCL2: B-cell lymphoma 2; BCL-xL: B-cell lymphoma extra large; CCND2: cyclin D2; CDK6: cyclin-dependent kinase 6; CYLD: cylindromatosis; G1/S: G1 and S-phase of cell cycle; MAPK: mitogen-activated protein kinase; MCL1: myeloid cell leukemia 1; MDM2: mouse double minute 2 homolog; NFkB: nuclear factor kB; PI3K: phosphoinositide 3-kinase; SMURF1: E3 ubiquitin-protein ligase.

being most down-regulated in GC (112). Low expression levels of miR-29c are associated with aggressive and progressive phenotypes of GC. In HGC-27 and MGC-803 GC cells, over-expression of miR-29 a, -b and -c suppresses cell growth, induces arrest of G1/S transition, and promotes apoptosis *in vitro* (112). Cyclin D2 (CCND2) and matrix metalloproteinase-2 (MMP2) were identified as direct targets of miR-29c (112). Intratumoral injection of synthetic miRs mimicking miRs-29a, -b and -c inhibit TG of subcutaneously implanted HGC-27 cell xenografts in mice (112). CCND2 forms complexes with cyclin-dependent kinases 4 and 6 (CDK4,6) and is required for G1/S transition (113). MMP2 is up-regulated in different types of tumors including GC (114). Expression of CCND2 is associated with shorter survival in patients with GC (113). Based on TCGA-derived data, miR-29c is

Figure 3. Expression of selected miRs in stomach adenocarcinoma compared to normal tissues. Data are shown for miR-1254, miR-125b, miR-133a, miR-133b, miR-137, miR-29a, miR-29b and miR-29c. Data from 436 tumor samples and 41 normal stomach samples derived from The Cancer Genome Atlas are shown. miR expression was quantified by RNA sequencing and is shown as log2 of normalized read counts. The red lines indicate lower versus higher expression. Expression data are shown as box plots. The line in the medium of the box represents the median value, the rectangles show the upper and lower 25% quartiles, and 50% of all data points are included in the greater rectangle. All of the data points, except for the outliers are located within the upper and lower whiskers.

down-regulated in GC specimens in comparison to corresponding normal tissues, in contrast to miRs- 29a and -b (Figure 3).

Mir-125b, -133b/a target MCL1 and BCL-xL. miR-125b (Figure 2) is down-regulated in GC and decreased levels of miR-125b correlate with advanced clinical stage, lymph node metastases, and poor clinical outcome in GC (115). Induced myeloid leukemia cell differentiation protein (MCL-1) was identified as a target of miR-125b (115). miR-125b inhibits proliferation of MGC-803 cells and TG in nude mice after subcutaneous implantation (115). miR-133b/a (Figure 2) is down-regulated by histone modification of its promoter in GC cells (116). miR-133b/a suppresses GC cell proliferation and promotes apoptosis, delays tumor formation, and reduces tumor size of GC xenografts in nude mice (116). MCL1 and BCL-xL (B-cell lymphoma-extra large) were identified as targets of miR-133b/a (116). MCL1 is a member of the anti-apoptotic BCL2 family, regulates cell growth, promotes EMT of GC cells, and its expression predicts poor outcome in GC patients (117, 118). BCL-xL is a multifunctional anti-apoptotic protein (119). BCL2 and BCL-xL mediate resistance to receptor-kinase targeted therapy in lung and gastric cancer (120). Based on TCGA data, miRs -125b, -133a and miR-133b are down-regulated in GC tissues in comparison to corresponding normal tissues (Figure 3).

miR-137 targets CDK6. miR-137 (Figure 2) expression correlates with better prognosis in GC patients (121). Ectopic

expression of miR-137 in GC cells inhibits proliferation *in vitro* and *in vivo* by targeting cyclin-dependent kinase 6 (CDK6) (121). CDK6 inhibitor PD0332991 mediates an anti-proliferative effect in GC cell lines, arrests them in the G1 phase and affects numerous oncogenic pathways such as p53, phosphoinositide-3 kinase (PI3K)/AKT, RAS/ERK, c-jun-N-terminal kinase (JNK)/MAPK, WNT/ β catenin, and SMAD signaling (122). CDK4,6 inhibitor palbociclib together with aromatase inhibitor letrozole has been approved for treatment of estrogen receptor positive breast cancer (123, 124). According to data derived from TCGA, miR-137 is down-regulated in GC tissues in comparison to corresponding normal tissues (Figure 3).

miR-181d targets CYLD. miR-181d (Figure 2) is down-regulated in GC and is a predictor for bad prognosis (125). miR-181d targets the cylindromatous gene (CYLD) and its expression inhibits proliferation and invasion of HGC-27 GC cells (125). In addition, it inhibits EMT and the PI3K/AKT pathway (125). Over-expression of miR-181 inhibits xenograft growth of HGC-27 cells after subcutaneous implantation into nude mice (125). CYLD is a lysine 63 deubiquitinylase, which modulates multiple signaling pathways such as NF κ B and MAPK by its catalytic activity on key intermediates of these pathways (126). In GC, down-regulation of CYLD by methylation of its promoter has been noticed (127).

miR-376-3p (BCL2). miR-376-3p (Figure 2) expression is reduced in GC tissues in comparison to adjacent normal

Figure 4. Tumor-suppressive miRNas targeting small GTPases and their regulatory proteins with activity in preclinical *in vivo* models: miRNas- *Let-7a*, *31*, *-124*, *-340*, *-148-3p*, *-329*, *-337*. ARHGAP10: RHO GTPase activating protein 10; CDC42: cell division control protein 42; CYSK: cytoskeleton; DOCK6: dedicator of cytokinesis 6; GAP: GTPase activating protein; GEF: guanine nucleotide exchange factor; RAB40C: ras-related protein 40C; RAC1: Ras-related C3 botulinum toxin substrate 1; RHOA: Ras homolog family member A; SRGAP1: SLIT/ROBO GTPase activating protein; TIAM1: T cell lymphoma invasion and metastasis1; WNT: WNT signaling.

tissues (128). Over-expression of miR-376-3p in SGC-7901 cells enhances apoptosis and inhibits TG of xenografts in nude mice (128). Over-expression of miR-376-3p decreases the levels of BCL2 (B-cell lymphoma 2) and increases the levels of pro-apoptotic protein BCL2 antagonist of cell death (BAD). However, it was not resolved whether BCL2 is a direct target of miR-376-3p (128). BCL2 has been shown to promote cell proliferation of GC cells (129). High Ki67/BCL2 index can predict disease free and overall survival in intestinal type GC (130).

miR-518 targets MDM2. miR-518 (Figure 2) is down-regulated in GC tissues and cell lines (131). In GC cell lines MKN45 and HGC-27 miR-mimics trigger apoptosis *in vitro* and *in vivo* (131). Mouse double minute 2 homolog (MDM2) has been identified as a target of miR-518 (131). MDM2 is an E3 ubiquitin-protein ligase which ubiquitinylates p53, triggering its degradation (131). miR-518 up-regulates p53, pro-apoptotic BCL2-associated protein X (BAX), activates caspase 3 and down-regulates BCL2 in GC cells (131). MDM2 up-regulation has been frequently observed in intestinal GC and correlates with nodal and distal metastases (132). An association between MDM2 amplification and tumorigenesis has been noted (133). Targeting p53/MDM2 interaction is an important effort for cancer drug discovery approaches (134).

miR-1254 targets SMURF1. miR-1254 (Figure 2) is down-regulated in human GC tissues and in GC-derived cell lines (135). Expression of miR-1254 inhibits proliferation, migration, and invasion of MGC-803 and SGC-7901 GC cell lines (135). SMAD ubiquitination regulatory factor 1 (SMURF1) was identified as a direct target of miR-1254 (135). SMURF1 is up-regulated in human GC tissues and cell lines (135). SMURF1 expression could partially reverse the effects of miR-1254 on GC cells (135). miR-1254 inhibits EMT and negatively regulates PI3K/AKT signaling by down-regulating SMURF1 (135). *In vivo*, miR-1254 mimics decrease TG of MGC-803 and SGC-7901 xenografts in nude mice (135). SMURF1 is an E3 ubiquitin ligase which regulates cell-cycle, apoptosis, metastasis, senescence, and genomic stability. It can act, in a context-dependent manner, as a tumor promoter or suppressor (136). According to TCGA-derived expression data, miR-1254 levels are very low in GC and also in corresponding normal tissues. Therefore, the degree of deregulation in GC cannot be determined based on these data (Figure 3).

Small GTPases and Proteins Modulating Their Activity

Let-7a targets RAB40C. Expression of the microRNA (lethal7-precursor) *Let-7a* (Figure 4) is reduced in GC tissues and cell lines in comparison to corresponding control tissues

and cell lines (137). Ectopic expression of let-7a mediates inhibition of proliferation, anchorage-dependent cell growth, and G1 arrest (137). BGC-823 cells transfected with let-7a mimics exhibit reduced TG after subcutaneous implantation into nude mice (137). RAB40C was identified as a direct target of miR Let-7a (137). RAB40C is a member of the RAS family of GTPases and is expressed in brain neurons and glia, is involved in vesicle transport in oligodendrocytes and plays an important role in tumorigenesis (138-140). Small GTPases, when activated transmit signaling to a variety of effector proteins after binding of GTP and hydrolyzing it to GDP (140). They are regulated by GAPs, GEFs (GTPase-activating proteins and Guanine nucleotide exchange factors) and RAS homology member family member (RHO) guanine dissociation inhibitors (GDIs). GAPs bind to activated G proteins and stimulate their GTPase activity, GEFs promote the exchange of GDP by GTP and GDIs sequester RHO-GTPases in the inactive state by inhibition of dissociation of inactive guanine nucleotides (140). The role of RAB-40C in GC remains to be investigated in further detail.

miR-31 targets RHOA. Expression of miR-31 (Figure 4) is negatively correlated with GC metastasis (141). miR-31 mimics inhibit migration of BGC-823 cells and inhibition of miR-31 promotes migration of SGC-7901 cells (141). Reduced lung metastasis after tail vein injection in nude mice was found when SGC-7901 GC cells were transfected with miR-31 mimics (141). RAS homology family member A (RHOA) was identified as a direct target of miR-31 (141). RHOA is a small GTPase which can activate RHO-associated, coiled-coil containing protein kinase which phosphorylates myosin light chain (MLC) and thus exacerbates the migration and invasion capability of GC cells (142). RHOA is also associated with cytoskeleton regulation such as actin stress fiber formation and actomyosin contractibility, cell migration, and metastasis in GC (143). RHOA has potential clinical significance as a prognostic marker in GC (144). Together with cell division control protein 42 homolog (CDC42) and RAS-related botulinum toxin substrate 1 (RAC1), RHOA is one of the best studied GTPases. Tractability of RHOA as a therapeutic target is a challenging issue, as holds true for all GTPases.

miRs-124, -340 target SRGAP1. miRs-124 and -340 (Figure 4) suppress cell growth, invasion, and colony formation of GC cell lines MKN45, MGC-803, and NCI-N87 (145). SLIT-roundabout (ROBO) GTPase activating protein (SRGAP1) is a downstream effector SLIT/ROBO signaling and was identified as a target of miRs-124 and -340 (145). SRGAP1 over-expression is associated with poor prognosis of GC patients (145). SRGAP1 promotes xenograft formation of GC cells in nude mice (145) and induces formation of CDC42-

GTP, RHOA-GTP, and RAC1-GTP complexes (145). Furthermore, SRGAP1 promotes WNT/ β catenin signaling thus establishing a link between SLIT/ROBO signaling and the WNT/ β catenin pathway (145). The downstream effectors CDC42, RHOA, and RAC1 are involved in filopodia formation by stress fibers and focal adhesion complexes, as well as formation of lamellipodia (146, 147). SLIT/ROBO signaling was first discovered in the central nervous system, later on also in cancer as a promoter of angiogenesis, inflammatory chemotaxis, tumor cell migration, and metastasis (148). In GC, miR-340 inhibits cell proliferation and apoptosis through regulation of NF κ B and suppressor of cytokine signaling (SOCS)/janus kinase (JAK)/STAT signaling (149, 150). miR-124 has been shown to suppress TG in GC xenografts in mice (151).

miR-148-3p targets DOCK6. miR-148-3p (Figure 4) targets and reduces the levels of dedicator of cytokines 6, a guanine nucleotide exchange factor (DOCK6) (152). DOCK6 expression is increased in GC tissues and indicates poor prognosis (152). DOCK6 increases proliferation, migration, and invasion of SGC-7901 SM GC cells by activation of RAC1 and CDC42 (152). In nude mice, over-expression of miR-148-3p in SGC-7901 M cells decreased lung and liver metastasis after tail vein injection, while DOCK6 over-expression reversed inhibition of metastasis (152). DOCK6 expression is negatively correlated with miR-148b expression in GC tissues (152). In mammals, 11 DOCK proteins have been identified as regulators of the actin cytoskeleton, cell adhesion and migration (153). The role of DOCK6 in GC needs further investigation.

miR-329 targets TIAM1. miR-329 (Figure 4) is down-regulated in GC and inhibits migration and invasion of GC cells MGC-803 and HGC-27 (154). *In vivo*, injection of HGC-27 cells together with miR-329 mimics inhibits TG in nude mice (154). T-cell lymphoma invasion and metastasis inducing protein 1 (TIAM1) was identified as a direct target of miR-329 (154). TIAM1 acts as a GEF for activation of RAC1, but also for CDC42, and to a lesser extent for RHOA (154). Protumoral activities of TIAM1 involve modulation of the cytoskeleton, cell polarity, membrane trafficking, cell migration, adhesion, cell growth, survival, carcinogenesis, and metastasis (155). But anti-cancer activity of TIAM1 has also been reported (155). Up-regulation of TIAM1 has been reported in GC and its involvement in cell migration and invasion (156, 157). The propensity of GEFs and GAPs as targets for anti-cancer therapy has been discussed (158).

miR-337 targets ARHGAP10. miR-337 (Figure 4) decreases the motility and viability of SGC-7901 GC cells, although it has no impact on their proliferation (159). RHO GTPase-activating protein 1 (ARHGAP10) was identified as a target

of miR-337 (159). ARHGAP10 restores viability and migration capacity of SGC-7901 cells (159). *In vivo*, SGC-7901 cells transfected with miR-337 give rise to reduced metastatic foci after tail vein injection in immunocompromized mice (159). RHO-GAPs are regulators of RHO-GTPase signaling pathways related to cytoskeletal dynamics, cell proliferation, and differentiation (160). ARHGAP10 contains a PDZ, a pleckstrin homology domain, and a RHO-GAP domain (160). However, opposite functional roles for ARHGAP10 have been reported. In lung cancer, ARHGAP10 inhibits proliferation, migration, invasion and WNT signaling (161). In colorectal cancer cells, ARHGAP10 inhibits proliferation and metastases *via* blocking of the RHOA/AKT signaling pathway (162). In ovarian cancer, ARHGAP10 is down-regulated and suppresses tumorigenicity (163).

Therapeutic Aspects

This review focusses on miRs that are down-regulated in GC and affect the expression of transcription factors, cell-cycle and apoptosis-related proteins, and of small GTPases and their regulatory proteins with demonstrated efficacy in preclinical *in vivo* models. Down-regulation of miRs can be due to aberrant miR processing, methylation of CpG islands in the promoter region and adjacent regions, and other epigenetic mechanisms (164-168). Replacement therapy can be achieved with miR-mimics, synthetic double-stranded RNAs that mimic the endogenous RNAs. Chemical modifications such as introduction of 2'-O-methyl, phosphorothioate and locked nucleic acids (LNA) can improve stability and targeting to the disease site (169-172). miR mimics or miRs can be injected intratumorally or systemically in designed formulations or as plasmid- or viral-derived vectors (169-172). Adeno-associated vectors can transduce target cells efficiently, do not integrate, are eliminated efficiently with minimal toxicity, and have emerged as vehicles for miR-replacement therapies (173, 174). A POC experiment revealed that restoration of miR let-7 was able to inhibit lung cancer in an orthotopic mouse model expressing KRAS G12D, an activating mutation of KRAS (175). Further important POC experiments reconstituting expression of miR-29b and 708-5p have been described in mouse lung cancer models (176, 177).

This review compiles published POC experiments for 37 selected *in vivo* miR replacement studies in GC-related *in vivo* models. The design of optimized delivery systems is of paramount importance in this context (169). Delivery systems based on modification of miRs with polyethylene glycol (PEG), neutral lipid emulsions, conjugation with N-acetyl-D-galactosamine, chitosan-nucleic acid conjugates, glucose-based-polymers such as cyclodextrin, dendrimers, synthetic polyethylenimine based vehicles, poly (lactide or glycolide)

particles or TargomiRs, bacterium-based vesicles with surface-based antibodies have been developed (169, 178).

Approaches towards applications of miR replacement therapy in cancer patients have focused on miR-34 (179) or miR-15/16 (180). miR-34 has been validated in numerous preclinical *in vitro* and *in vivo* studies as a candidate for replacement therapy (181). This holds true for colorectal, prostate, breast, liver, and lung cancer as well as osteosarcoma and haematological neoplasms (181). miR-34 inhibits crucial oncogenic and metastatic pathways such as EMT mediated by transcription factors SNAIL, SLUG and ZEB1,2, NOTCH-, WNT-, IL6R- and TGF β /SMAD signaling (181). MRX 34 (Mirna Therapeutics), an amphoteric, lipid nanoparticle filled with miR-34 mimics, has been evaluated in a Phase I clinical study (NCT01829971) in 155 participants in several solid tumors and haematological malignancies. That study, however, had to be terminated due to immune-related side effects in five patients (181, 182). As outlined, in GC, miR-34 targets transcription factor YY1 and may be a possible agent for replacement therapy.

The other ongoing clinical study for miR-replacement therapy is based on epidermal growth factor receptor (EGFR)-coated bacterial minicells (EnGene IC) expressing mimics corresponding to the miR-15/107 consensus sequence (miR-16 mimics). The delivery vehicles are nanocells also referred to as TargomiRs. The Phase I study in patients with metastatic pleural mesothelioma and advanced non-small cell lung carcinoma (NSCLC) is referred to as the mesomiR-1 study (180, 183). In preclinical experiments, expression of miR-16 in mesothelioma cell lines had a tumor-suppressive effect through induction of apoptosis by down-regulation of BCL2 and CCND1 (184). In a phase I study, 27 patients were enrolled with an objective response and stabilization of disease in 15 patients (183).

As of today, several issues that hamper the therapeutic application of miR-related agents remain to be resolved (185-192). These issues are not discussed in detail in this review.

Conclusion

Our comprehensive review of GC-associated miRs revealed 25 down-regulated miRs that target transcription factors, 7 targeting cell-cycle/apoptosis-related genes, and 5 directed against small GTPase-related and -associated molecules such as GEFs and GAPs. These might present as candidates for potential therapeutic intervention in GC patients, in the form of replacement therapy or inhibition of the corresponding up-regulated targets. The applicability of such replacement therapies is still limited by technical hurdles as described above. For target prioritization issues such as prevalence, prognostic relevance, druggability and consistent or context-dependent functional properties are important parameters for ranking. In case of transcription factors, tractability is critical because mode of intervention is difficult because it would

involve inhibition of DNA binding or of co-factor protein-protein interactions (193). Also, modulation of the levels of transcription factors by interfering with ubiquitinylation and subsequent proteasome degradation might be considered. Proteolysis targeting chimeras (PROTACS) directed against intrinsically disordered regions of transcription factors with Cys-reactive inhibitors and another moiety engaging an E3 ubiquitin ligase are emerging agents for interference (194). The druggability of small GTPase related molecules, GEFs and GAPs has to be categorized as critical, despite of encouraging recent developments (195, 196). The functions of TIAM1 (miR-329), ARHGAP10 (miR-337) and SMURF1 (miR-1254) are context-dependent as outlined. For NR2F2 (miR-27b), E2F2, RHOA (miR-31) and CYLD (miR-181d) contradictory functions have been published as described in the previous text. Prognostic data are available for miR-29 (CCND2), miR-105, -138c (SOX9, SOX4), miR-124, -130 (SRGAP1), miR-133 b/a miR-136 (HOXC10), miR-141, -200c (ZEB1, ZEB2), miR-145 (ETS1), miR-186 (HIF-1 α), miR-320 (FOXM1), miR-489 (PROX1), miR-518 (MDM2) and miR-1297 (CREB1). Taken together miR-133b/a (MCL1) and miR-518 (MDM2) might present as promising targets. However, more GC specific target validation experiments are needed to derive firm conclusions. Broad drug discovery programmes for MCL1 and p53/MDM2 and clinical studies on other indications are ongoing (197-199).

Conflicts of Interest

FB, SA, and UB are and UHW was an employee of Roche.

Authors' Contributions

FB, SA, UB and UHW jointly designed and prepared the manuscript.

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