Review

MicroRNAs and Corresponding Targets in Esophageal Cancer as Shown *In Vitro* and *In Vivo* in Preclinical Models

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Abstract. *Squamous cell carcinoma of the esophagus is associated with a dismal prognosis. Therefore, identification of new targets and implementation of new treatment modalities are issues of paramount importance. Based on a survey of the literature, we identified microRNAs conferring antitumoral activity in preclinical in vivo experiments. In the category of miRs targeting secreted factors and transmembrane receptors, four miRs were up-regulated and 10 were down-regulated compared with five out of nine in the category transcription factors, and six miRs were down-regulated in the category enzymes, including metabolic enzymes. The down-regulated miRs have targets which can be inhibited by small molecules or antibody-related entities, or re-expressed by reconstitution therapy. Up-regulated miRs have targets which can be reconstituted with small molecules or inhibited with antagomirs.*

More than 450,000 patients are affected by esophageal cancer worldwide (1). The highest incidence is found in eastern Asia, eastern and southern Africa, and southern Europe (1). In the USA, the disease claimed 16, 170 deaths in 2020 (2). Esophageal cancer is one of the most lethal types of cancer and surgical resection, chemotherapy and radiotherapy are primary treatments but have limited efficacy and severe side-effects (3). Two histological subtypes have been identified: esophageal adenocarcinoma and esophageal

squamous cell carcinoma (ESCC) as epidemiologically and biologically distinct types of cancer (4). ESCC is the major histological subtype and accounts for 80% of esophageal cancer worldwide (4). However, the incidence of esophageal adenocarcinoma and ESCC vary with geographic location (4). Barrett's esophagus is a benign precursor lesion of esophageal adenocarcinoma (5).

Characterization of the genomic landscape of ESCC has revealed heterogeneity, and mutations in pathways of growth factor receptors, cell-cycle regulation, apoptosis, angiogenesis and DNA repair (6, 7). The US Food and Drug Administration recently approved pembrolizumab and nivolumab, which both target programmed death 1 for immunotherapeutic intervention for advanced ESCC. Pembrolizumab was approved for treatment of unresectable/metastatic tumors with high microsatellite instability, and nivolumab for unresectable, advanced or recurrent tumors (8, 9). Nevertheless, there is an urgent need to identify new targets and treatment modalities for ESCC. In this review, we focus on microRNAs (miRs) shown to be ESCC-related in preclinical *in vivo* systems for target identification and as new treatment modalities through inhibition or reconstitution of function for ESCC.

MicroRNAs and Cancer

miRs are small regulatory RNAs that derive from hairpin regions of precursor transcripts (10). Each miR associates with an Argonaute protein, forming a silencing complex which binds to complementary sequences of target transcripts and promotes destabilization or translational repression of the bound transcripts (10). miRs can interfere with several targets and act as oncogenes or tumor suppressors in a context-dependent manner (11, 12). They play a role in all aspects of cancer such as proliferation, apoptosis, invasion, metastasis and angiogenesis (13-16). In proof-of-concept experiments it has been shown that deletion of *miR-15* and *miR-16* induced B-cell lymphoma in mice by targeting BCL2 apoptosis regulator (BCL2) (17) and expression of *miR-17* in the liver of transgenic mice caused hepatocellular carcinoma (18). The

This article is freely accessible online.

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Key Words: miR-based target identification, miR-related treatment modalities, preclinical *in vivo* models, squamous cell esophageal cancer, review.

roles of miRs in ESCC have been summarized in several reviews (19-21). In this review, we focus on miRs in preclinical *in vivo* ESCC models in order to identify targets for therapeutic intervention and to explore new entities for therapeutic intervention by inhibition of deregulated miRs or replacement therapy with miR mimics.

miRs Targeting Secreted Factors and Transmembrane Receptors in *In Vivo* Models

Up-regulated miRs (Figure 1A).

miR-19a [targeting tumor necrosis factor α (TNF α)]. *miR-19a* induced proliferation of ESCC cell lines EC109, EC 9706 and KYSE150 (22). An antisense oligo directed against *miR-19a* induced apoptosis in EC9706 cells (22). Knock-down of *miR-19a* inhibited *in vivo* tumorigenicity of EC9706 cells in nude mice (22). TNF α was identified as a direct target of *miR-19a* (22). Pro- and anti-tumoral effects, such as stimulation of cancer progression and metastasis, direct cytotoxicity to tumor cells and stimulation of the immune response against cancer, have been reported (23-26). Therefore, the tumor-inhibitory function of TNF α in ESCC has to be resolved in more detail.

miR-25 (targeting E-cadherin). Overexpression of *miR-25* in patients with ESCC was associated with lymph node metastasis and poor survival (27). *miR-25* induced migration but not proliferation in KYSE150 ESCCs (27). Targeting *miR-25* reversed epithelial-mesenchymal transition (EMT) transition in ESCCs *in vitro* (27). E-Cadherin was identified as a direct target of *miR-25* (27). Up-regulation of *miR-25* induced lung metastases after tail vein injection of EC-109 ESCC cells in immunocompromised mice (27). Down-regulation of E-cadherin was correlated with development and progression of cancer, high tumor grade and low patient survival (28, 29). It has been shown that modulation of expression of E-cadherin promotes migration of ESCC cells (30). However, due to specificity issues inherent to up-regulation of E-cadherin with small molecules, targeting E-cadherin is a difficult issue from a drug-discovery point of view.

miR-483-3p [targeting etoposide-induced 2.4 transcript (EI24)]. *miR-483-3p* was overexpressed in ESCC, promoted proliferation, G₁/G₂ transition and migration of ESCCs, and inhibited sensitivity of ESCC to chemotherapy (31). *miR-483-3p* promoted growth of ESCC xenografts in immunocompromised mice (31). *EI24* has been identified as a direct target of *miR-483-3p* (31). *EI24*, a p53-response protein, contains six transmembrane domains and suppresses cell growth through caspase 9 and mitochondrial pathways including in ESCC (32, 33). Furthermore, *EI24* has been shown to contribute to EMT (34).

miR-584k [targeting A disintegrin and metalloprotease with thrombospondin motifs 1 (ADAMTS1)]. *miR-548k* overexpression correlated with poor prognosis of patients with ESCC (35). *miR-548k* mediated proliferation and cell-cycle progression of KYSE30 and KYSE150 ESCCs and induced migration and tube formation by human dermal lymphatic endothelial cells (35). In nude mice implanted with KYSE30-derived ESCCs transfected with *miR-548k*, lymphangiogenesis, increased microlymphatic density and metastasis to lymph nodes were observed (35). Tail vein injection experiments indicated that *miR-548k* promotes lung metastasis (35). *ADAMTS1* was identified as a target of *miR-548* (35, 36). Overexpression of *miR-548k* promoted tyrosine phosphorylation in dermal lymphatic endothelial cells (35). Vascular endothelial growth factor receptor 3 (VEGFR3), a stimulator of lymphangiogenesis and promoter of lymphatic metastasis, is stimulated by *ADAMTS1* (36-39). *miR-548k* also down-regulates Kruppel-like factor 10 (KLF10), a repressor of epidermal growth factor receptor (EGFR) (40).

Down-regulated miRs (Figure 1B).

miR-126 (targeting VEGFA). Lower expression of *miR-126* in ESCC tissues and cell lines compared to corresponding normal tissues was observed (41). *VEGFA* was identified as a target of *miR-126* (41). *miR-126* inhibited proliferation of JH-Eso Ad1, OE19 and OE33 ESCC cells (41). In nude mice, tumor growth was inhibited in OE33 cells transfected with *miR-126* (41). *VEGFA* can increase permeabilization of blood vessels and growth of new blood vessels (42, 43). Targeting of *VEGFA* with monoclonal antibodies has been pursued successfully in clinical trials, leading to approval for several tumor indications, but not ESCC (44).

miR-133b (targeting EGFR). *miR-133b* repressed proliferation, apoptosis, anchorage-independent growth and EMT of KYSE150 and ECA109 ESCCs and its expression was reduced in ESCC tissues (45). *miR-133b* inhibited tumor growth and lung metastases of KYSE150 and ECA109 ESCCs in nude mice (45). *EGFR* was identified as a target of *miR-133b* (45). *miR-133b* was shown to inhibit anchorage-independent growth, migration and invasion of ESCC *via* integrin β 4 (INTB4)/focal kinase/growth-factor receptor bound protein 2, AKT serine/threonine kinase 1 and extracellular signal-regulated kinase signaling pathways (45). Gene amplification, aberrant activation and activation mutations of *EGFR* have been observed in several types of cancer (46, 47). *EGFR* has been identified as an important target for ESCC (48): 70-88% of patients with ESCC show high expression of *EGFR* and its high expression correlates with poor prognosis (49, 50).

miR-193a-5p [targeting human epidermal growth factor receptor 2 (HER2)]. *miR-193a-5p* inhibited *HER2* expression and enhanced radiosensitivity of ESCCs *in vitro*

Figure 1. Up-regulated (A) and down-regulated (B) miRs targeting secreted factors and transmembrane receptors in esophageal cancer cells in preclinical *in vivo* systems. ADAMTS1: A disintegrin and metalloprotease with thrombospondin motifs 1; CD44, 47, 133: cluster of differentiation 44, 47, 133; EGFR: epidermal growth factor receptor; E124: etoposide-induced 2.4 transcript; HER2: human epidermal growth factor receptor 2; IGF1R: insulin growth factor-like receptor 1; INTα6: integrin α6; INTβ6: integrin β6; INV: invasion; MET: metastasis; PROL: proliferation; RAGE: receptor for advanced glycation end-products; SARA: SMAD anchor for receptor activation; TG: tumor growth; TGFβR2: transforming growth factor receptor 2; TNFα: tumor necrosis factor α; VEGFA: vascular endothelial growth factor A.

and *in vivo* in mice (51). It reduced colony formation in KYSE70 and KYSE510 ESCCs and inhibited tumor growth by down-regulation of *HER2* *in vitro* and *in vivo* (51). High expression of *miR-193a-5p* was correlated with successful chemoradiation treatment of ESCC (51). *HER2* was also targeted in an orthotopic model of esophageal carcinoma (52). *HER2* is up-regulated in 10-20% of ESCC and its up-regulation is correlated with worse prognosis (53-56).

miR-375 [targeting insulin-growth factor like 1 receptor (*IGF1R*)]. Down-regulation of *miR-375* correlated with advanced stage, distant metastasis, poor overall survival and disease-free survival in patients with ESCC (57). Down-regulation of *miR-375* in ESCC was due to promoter methylation (57). *IGF1R* has been identified as a direct target of *miR-375* (57). *miR-375* suppressed proliferation and invasion of KYSE10 and KYSE30 ESCCs and their

metastasis to the liver after tail vein injection into nude mice (57). In clinical specimens of ESCC, *IGF1R* expression was negatively correlated with *miR-375* expression (57). Targeting of the *IGF1R* pathway has been pursued in many types of cancer (58). In ESCC, overexpression of *IGF1R* was noted in 60% of tumors in patients (59). *IGF1R* is a marker for prognosis and a potential therapeutic target for ESCC (60, 61). The *IGF1R* pathway has been identified as a key axis in progression of ESCC (62). Antitumoral effects have been observed with figitumumab, a monoclonal antibody directed against *IGF1R* in several preclinical *in vitro* and *in vivo* models of ESCC (63).

miR-17/20a [targeting transforming growth factor β receptor 2 (*TGFRβ2*) and *SMAD* anchor for receptor activation (*SARA*)]. Down-regulation of *miR-17/20a* correlated with ESCC lymph node metastasis and inhibited migration and

invasion of 30D and 180-U ESCCs (64). *miR-17/20a* suppressed lung metastasis of 30D cells after tail vein injection into nude mice (64). *miR-17/20a* did not influence proliferation and apoptosis of ESCCs (64). *TGFR β 2* and *SARA* were identified as *bona fide* targets of *miR-17/20a* (64). A heterotrimeric SMAD2, -3, -4 complex is translocated into the nucleus to regulate transcription of genes such as *INTB6*, which mediates migration and invasion (64, 65). The other target of *miR-17/20a*, *SARA*, recruits SMAD2/SMAD3 complexes to *TGFR β 2* at intracellular membranes (66). However, *TGF β* signaling can exert pro- as well as antitumoral effects in a context-dependent manner and therefore has to be investigated in further detail in ESCC (67, 68).

miR-92b (targeting *INTav*). *miR-92b* inhibited lymph node metastasis and was associated with favorable prognosis in patients with ESCC (69). *miR-92b* inhibited migration and invasion of 30D ESCCs *in vitro* (69). *In vivo*, *miR-92b* inhibited invasion into the peri-esophageal muscle after orthotopic implantation of 30D cells into nude mice (69). In the tail vein injection model, *miR-92b* inhibited lung metastasis (69). *INTav* has been identified as a *bone fide* target of *miR-92b* (69). Furthermore, *miR-92b* reduced phosphorylation of focal adhesion kinase and reduced activation of RAS-related C3 botulinum toxin substrate (RAC1), both essential mediators of cellular motility in ESCCs (69, 70). Integrins consist of 18 α and 8 β transmembrane receptors, inclusive 24 heterodimers, which can cross-link components of the extracellular matrix with the cytoskeleton and thus have an impact on invasion and metastasis of tumor cells (71, 72).

miR-34a [targeting cluster of differentiation 44 CD44)]. *miR-34a* was down-regulated in ESCC tissues and cell lines and inhibited invasion and migration of ECA109 and TE-13 ESCC cells (73). *miR-34* inhibited tumor growth and metastasis in nude mice (73). CD44 was identified as a target of *miR-34a* (73). CD44 is a transmembrane protein with hyaluronic acid as the major ligand, resulting in activation of pathways involved in proliferation, survival, cytoskeletal changes, motility and metastasis (74, 75). CD44 standard form and several splice variants which contain additional peptide motifs that can interact with growth factors and cytokines at the cell surface may play a role in EMT and adaptive plasticity of cancer cells (76, 77). It has been shown that up-regulation of CD44 in E-cadherin-negative esophageal cancer cells results in activation of invasion (78). Tumor-initiating cells in ESCC express high levels of CD44 (79) and overexpression of CD44 is associated with poor prognosis in patients with ESCC (80).

miR-133a (targeting *CD47*). CD47 expression in ESCC was associated with lymph node metastasis (81). Expression of CD47 was significantly lower in ESCC samples in

comparison to corresponding non-cancerous tissues (81). CD47 was identified as a target of *miR-133a* (81). Pre-*miR-133a* strongly inhibited the tumorigenic potential of TE-8 ESCC *in vivo* in nude mice (81). CD47 is a transmembrane molecule which inhibits phagocytosis and therefore is a target which has received much attention in translational oncology (82-84). It was shown that following blocking of CD47 with monoclonal antibodies, ESCCs were phagocytosed by M2 macrophages (85).

miR-377 (targeting *CD133* and *VEGF*). Down-regulation of *miR-377* correlated with poor chemotherapy response and poor survival in patients with ESCC (86). *miR-377* inhibited tumor-initiating cell properties (86). *CD133* and *VEGF* were identified as direct targets of *miR-377* (86). In the tail vein injection model, *miR-377* inhibited lung colonization of KYSE270 cells in mice (86). A systemic formulation of a *miR-377* mimic inhibited tumor growth, angiogenesis and metastasis of ESCC cells in nude mice (86). CD133 is a marker of tumor-initiating cells in cancer, but its quantitation has been hampered by the inability of current antibodies to detect CD133 variants and deglycosylated epitopes (87, 88). CD133 is a regulator of metastasis through cancer stem cells (89). CD133 promotes stemness in ESCC cells and its higher expression is associated with lymph node metastasis, clinical stage and histopathological grade of ESCC (90, 91). As outlined previously, VEGFA is a validated target for several types of cancer (42).

miR-185 [targeting receptor for advanced glycation end-products (RAGE)]. Overexpression of *miR-185* suppressed migration and invasion of TE-11 and ECA109 ESCCs *in vitro* (92). In the tail vein metastasis model, *miR-185* suppressed metastasis of ECA109 cells (92). In patients with ESCC, the level of plasma *miR-185* was found to be decreased (92). RAGE was identified as a target of *miR-185* (92). RAGE, a 35-kDa transmembrane receptor of the immuno-globulin super-family, and its ligands, high motility group box 1 (HMGB1) and S100 group of proteins, release cytokines after their interaction. Transcription factors which are involved in TG and survival, EMT and metastasis are also activated. RAGE is being evaluated as a target for cancer therapy (93, 94). Expression levels of RAGE are related to poor prognosis in patients with ESCC (95).

miRs Targeting Transcription Factors

Up-regulated miRs (Figure 2A).

miR-7-5p [targeting *Kruppel-like factor 4 (KLF4)*]. *miR-7-5p* was up-regulated in ESCC tissues and inhibited proliferation of ECA109 and TE-9 ESCCs (96). A *miR-7-5p* antagonist induced apoptosis in ECA109 and TE-9 cells and suppressed migration and invasion of ECA109 cells (96). A *miR-7-5p* antagonist inhibited tumor growth of ECA109

Figure 2. Up-regulated (A) and down-regulated (B) miRs targeting transcription factors in esophageal cancer cells in preclinical *in vivo* systems. AKT: Serine-threonine kinase AKT; ARID3A: AT-rich interactive domain-containing protein 3A; CXXC5: CXX-type zinc finger protein 5; DDP res: cisplatin resistance; EMT: epithelial-mesenchymal transition; FOXK2: forkhead box protein K2; FOXO31: forkhead-box protein 31; FOXM1: forkhead box protein M1; GSK3 β : glycogen synthase kinase 3 β ; INV: invasion; KLF4: Krüppel-like factor 4; MAPK: mitogen-activated protein kinase; MET: metastasis; MYC: transcription factor MYC; mTOR: mechanistic target of rapamycin; p38: mitogen-activated protein kinase p38; PITX2: paired-like homeodomain transcription factor 2; PPAR γ : peroxisome proliferator-activated receptor γ ; PROL: proliferation; SMAD4: signaling protein SMAD4; SNAI2: snail family transcriptional repressor 2; SOX4: sex determining region Y-box 4; STAT3: signal transducer and activator of transcription 3; TG: tumor growth; ZEB1: zinc finger E-box binding homeobox 2.

cells *in vivo* (96). KLF4 was identified as a direct target of *miR-7-5p* (96). KLF4 is a member of the KLF family of zinc finger transcription factors and contains three C2H2 zinc fingers. KLF4 is a stem cell factor which, together with octamer-binding transcription factor 4, SOX2, homeobox protein NANOG and transcription factor MYC, is involved in the induction of pluripotent stem cells (97). Most studies suggest that KLF4 acts as a tumor suppressor, but pro-tumorigenic activity of KLF4 has also been reported (98). KLF4 promoted ESCC differentiation by up-regulation of keratin 13 expression (99). In ESCC, KLF4 was shown to act as a tumor suppressor and was correlated with good prognosis (100).

miR-10b [targeting peroxisome proliferator-activated receptor gamma (PPAR γ)]. *miR-10b* was up-regulated in patients with

ESCC and targeted PPAR γ (101). Suppression of *miR-10b* in ESCC cell lines enhanced chemosensitivity to cisplatin *in vitro* and *in vivo* (101). PPAR γ enhanced resistance to cisplatin by activating AKT/mechanistic target of rapamycin (mTOR)/ribosomal protein70 S6 kinase (p70S6K) signaling (101). PPAR γ is a member of the nuclear receptor superfamily and was shown to act as a ligand-inducible transcription factor which can exert tumor-suppressive and pro-tumorigenic effects (102, 103). It has been shown that PPAR γ ligands suppress proliferation and induce apoptosis of ESCCs by inhibiting toll-like receptor 4-dependent mitogen-activated protein kinase signaling (104). Reduced PPAR γ expression is correlated with poor prognosis in patients with ESCC (105).

miR-32 (targeting CXXC5-type zinc finger protein 5). Increased expression of *miR-32* has been noted in ESCC

tissues and cells (106). Down-regulation of *miR-32* inhibited migration and invasion of EC9706 and KYSE450 ESCCs (106). *In vivo*, *miR-32* inhibitors reduce tumor weight and number of metastatic nodules (106). CXXC5-type zinc finger protein 5 (CXXC5) was identified as a target of *miR-32* (85). *miR-32* inhibitors reduced migration, invasion, EMT and TGF β signaling (106). CXXC5 inhibited WNT/ β catenin signaling, induced apoptosis by stimulating TGF β /SMAD signaling and activated DNA repair *via* the serine-threonine kinase ataxic telangiectasia mutated/p53 pathway (107-109). In addition, CXXC5 promoted TGF β induced cell-cycle arrest (110). The role of CXXC5 in ESCC remains to be resolved in further detail.

miR-99b/let7a/miR-125a [targeting AT-rich interaction domain 3A (ARID3A)]. The *miR-99b/let7a/miR-125a* cluster promoted ESCC migration and invasion *in vitro* and induced experimental metastases *in vivo* (111). Transcription factor zinc finger E-box binding homeobox factor 1 (ZEB1) bound to the promoter of this cluster and regulated its transcription (111). ARID3A was identified as a direct target of *miR-99b/let7a/miR-125a* (111). ARID3A is a transcription factor which regulates chromatin accessibility, proliferation, differentiation and is critical for B-cell development (112). ARID3A expression was found to be reduced in ESCC compared to normal corresponding tissues (113). ARID3A has been shown to be involved in carcinogenesis and development of ESCC (114).

miR-602 [targeting forkhead box protein K2 (FOXK2)]. *miR-602* was increased in ESCC tissues and its expression level significantly correlated with poor survival (115). DNA hypomethylation was involved in increased expression of *miR-602* in ESCC (115). *miR-602* promoted proliferation, colony formation, migration and invasion by KYSE 150 and KYSE 450 ESCCs (115). In KYSE 450 cells transfected with *miR-602*, tumor growth was significantly accelerated (115). *miR-602* antagomir directly injected into the tumor led to slower tumor growth (115). In the tail vein assay, *miR-602* induced increased metastasis to the lungs, to liver, bones and adrenal glands (115). FOXK2 was identified as a target of *miR-602* (116). FOXK2 binds to purine-rich motifs on DNA and is involved in proliferation, survival, DNA damage, metabolism, invasion, migration and metastasis. However, the function of FOXK2 is context-dependent and depends on the tumor type (117). Down-regulation of FOXK2 was associated with poor prognosis in patients with gastric cancer (118).

Down-regulated miRs (Figure 2B).

miR-124 [targeting signal transducer and activator of transcription 3 (STAT3)]. *miR-124* was suppressed in ESCC tissues and cell lines, inhibited proliferation and migration and induced apoptosis in ECA190 and TE-1 ESCCs (119).

In ECA109 engrafted tumors, *miR-124* inhibited growth (119). STAT3 was identified as a direct target of *miR-124* (119). Activation of STAT3 by phosphorylation leads to its dimer formation, translocation into the nucleus, recognition of STAT3 binding elements and transcriptional activation of target genes. STAT3 regulates expression of genes related to the cell cycle, survival and the immune response, and is associated with progression and malignancy in several types of cancer (120, 121). STAT3 is being evaluated as a potential target for treatment of cancer (122). It has been shown that STAT3 is constitutively activated in ESCC tissues (123), inhibits apoptosis (124) and mediates proliferation and migration of ESCCs (125).

miR-130-3p (targeting SMAD4). *miR-130a-3p* directly targeted SMAD4 in EC-1 ESCCs (126). *miR-130a-3p* inhibited tumor axillary lymph node metastasis in nude mice (126). *miR-130a-3p* inhibited EMT, invasion, and migration induced by TGF β in EC-1 cells (126). Restoration of SMAD4 expression rescued *miR-130a-3p*-suppressed EMT, invasion and migration (126). SMAD4 forms heterotrimeric complexes with SMAD2 and SMAD3 which are translocated into the nucleus and regulate expression of selected genes (127). SMAD4 is required for TGF β -induced EMT (128). In healthy and early-stage cancer cells, TGF β signaling has tumor-suppressive functions; in late-stage cancer, it can promote tumor progression, metastasis and chemotherapy resistance (129, 130).

miR-133a (targeting SOX4). *miR-133a* was down-regulated in ESCC tissues and cell lines KYSE150, KYSE510, EC9706 and TE13 in comparison to SHEE non-transformed esophageal cell line (131). *miR-133a* inhibited proliferation, migration and invasion of ESCCs as mentioned above (131). *In vivo*, *miR-133a* inhibited tumorigenicity of TE13 cells in a mouse xenograft model (131). SOX4 was identified as a direct target of *miR-133a* (131). SOX4 levels inversely correlated with *miR-133a* in ESCC tissues (131). SOX4 is up-regulated in many types of cancer and contributes to cellular transformation, cell survival and metastasis (132, 133). SOX4 was found to induce WNT signaling and EMT (134, 135). The role of SOX4 in ESCC remains to be explored in further detail.

miR-145 (targeting MYC). *miR-145* was down-regulated in ESCC tissues and suppressed proliferation, invasion and tumor growth of ESCC xenografts by targeting MYC (136). MYC is a transcription factor which increases proliferation, cell-growth and inactivates cell-cycle inhibitors (137-139). MYC can be amplified in ESCC and its high expression is significantly correlated with poor prognosis in patients with ESCC (140, 141). Compounds identified by several MYC inhibition approaches are close to clinical trials (142).

miR-150 (targeting ZEB1). Low expression of *miR-150* contributed to malignant potential, lymph node metastasis, lymphatic and venous invasion, clinical staging and poor prognosis of patients with ESCC (143). *miR-150* inhibited proliferation, migration and regulated morphology of TE-8 ESCCs (143). In a TE-8 xenograft model, *miR-150* inhibited tumor growth (143). *ZEB1* was identified as a target of *miR-150* (143). *ZEB1* contains seven zinc-fingers and one homeodomain and is a transcription factor that controls EMT (144). Aberrant expression of *ZEB1* fosters invasion, migration and metastasis (145). It has been shown that *ZEB1* promotes invasiveness of ESCC and confers an unfavorable prognosis in patients with ESCC (146).

miR-204 (targeting FOXM1). *miR-204* was down-regulated in ESCC tissues in comparison to corresponding normal tissues (147). *miR-204* inversely regulated EMT in EC109 and TE10 ESCCs (147). Overexpression of *miR-204* suppressed growth of EC109 cells *in vivo* (147). *FOXM1* was identified as a direct target of *miR-204* (147). *FOXM1* is a member of the family of FOXO transcription factors which are deregulated in many diseases, including cancer (148). *FOXM1* is required for proliferation of many normal cells and as a master regulator is implicated in all hallmarks of cancer (149). *FOXM1* is overexpressed in many types of tumors. Its oncogenic role is mediated by interaction with β -catenin and SMADs to induce WNT and TGF β signaling pathways (150). Silencing of *FOXM1* inhibited proliferation and migration of ESCCs (151). In ESCC, *FOXM1* can activate phosphoinositide-3 kinase (PI3K)/AKT signaling and its expression was correlated with poor prognosis (151).

miR-507 [targeting nuclear factor erythroid 2-related factor 2 (NRF2)]. Administration of *miR-507* alone or in combination with cisplatin inhibited tumor growth *in vivo* (152). *NRF2*, a basic leucine zipper protein transcription factor, was identified as a target of *miR-507* (153). Under high oxidative stress levels, the *NRF2* pathway is activated. Normally, *NRF2* is degraded by Kelch-like-ECH-associated protein (KEAP1) and Cullin3 through ubiquitinylation. Non-ubiquitinylation *NRF2* is translocated into the nucleus, combines with musculoaponeurotic fibrosarcoma transcription factors and binds to anti-oxidative response elements in the promoter regions of anti-oxidative stress genes (153). Tumor-suppressive as well as oncogenic functions have been assigned to *NRF2* (154-156). In *NRF2*-addicted cancer, *NRF2* is constitutively activated due to somatic mutations in *KEAP1* or *NRF2* and other mechanisms that disrupt binding of *KEAP1* to *NRF2* (157). In ESCC, *NRF2* has been shown to induce proliferation and to be associated with radio- and chemotherapy resistance (158, 159).

miR-630 [targeting snail family transcriptional repressor 2 (SNAIL2)]. Reduced *miR-630* expression was associated with

poor survival in patients with ESCC (160, 161). Transcription factor *SNAIL2*, also known as SLUG, has been identified as a direct target of *miR-630* (160). Ectopic expression of *miR-630* inhibited proliferation, invasion, EMT and metastasis of ESCC cell lines *in vitro* and *in vivo*. *SNAIL2* plays a role in EMT and mediates anti-apoptotic activity (162, 163). Independently it has been shown that its down-regulation by RNA interference inhibited invasion and growth of ESCC (164).

miR-664a [targeting paired-like homeodomain transcription factor 2 (PITX2)]. Low expression of *miR-664a* correlated with tumor recurrence or metastasis in patient samples (165). *miR-664a* overexpression in KYSE-140 and -109 ESCCs reduced cell growth, colony formation, migration and invasion *in vitro* (165). Tumor growth *in vivo* was inhibited by *miR-664* in KYSE-140 and ECA109 cells in immunocompromised mice (165). The number and size of lung metastases of these cell lines in mice were dramatically reduced by *miR-664* (165). *PITX2* was identified as a direct target of *miR-664a* (165). *miR-664a* was down-regulated by promoter hypermethylation and inhibited the WNT/ β catenin pathway by targeting *PITX2* in ESCCs (165). *PITX2* acts as a transcription factor and participates in muscle formation (166, 167). Up-regulation of *miR-664a* reduced ESCC cell stem-like traits (168).

miRs Targeting Metabolic Enzymes (Figure 3)

miR-144 [targeting p53-inducible glycolysis and apoptosis regulator (TIGAR)]. *miR-144* was down-regulated in patients with ESCC and correlated with poor prognosis (169). Proliferation of EC9706 and ECA109 ESCCs was inhibited by *miR-144*, which was associated with a pro-apoptotic effect (169). *In vivo*, *miR-144* inhibited tumor growth of xenografts of these cell lines (169). *TIGAR* was identified as a direct target of *miR-144* (169). *TIGAR* acts as a fructose-2,6 biphosphatase and as a regulator of glucose breakdown (170). In some types of cancer, *TIGAR* is aberrantly up-regulated and promotes carcinoma growth by metabolic intermediates derived from the pentose phosphate pathway (171). *TIGAR* also reprograms glucose metabolism from glycolysis to the glutamine pathway through AMP-activated kinase (171). In *TIGAR*-overexpressing xenografts and patient-derived xenografts, efficacy was significantly enhanced when a glutaminase inhibitor was combined with chemotherapy agents (172).

miR-203a-5p [targeting ubiquitin-specific peptidase 26 (USP26)]. *miR-203-5p* was significantly down-regulated in esophageal tumor tissue (173). Overexpression of *miR-203a-5p* inhibited invasion and migration of KYSE150 and TE-1 ESCCs (173). Nude mice injected with a *miR-203-5p* mimic showed reduced lung metastasis of KYSE150 cells after tail

Figure 3. Down-regulated miRNAs targeting enzymes in esophageal cancer cells mediating efficacy in preclinical in vivo systems DNA polβ: DNA polymerase β; LDHB: lactate dehydrogenase B; MET: metastasis; MTDH1: metadherin 1; OGT: O-linked-N-acetylglucosaminacylation transferase; PROL: proliferation; PSAT1: phosphoserine aminotransferase 1; INV: invasion; TG: tumor growth; TIGAR: p53-inducible glycolysis and apoptosis regulator; USP26: ubiquitin-specific protease 26.

vein injection (173). *miR-203a-5p* targets *USP26* which stabilizes EMT-related transcription factor *SNAI1* (173). In normal tissues, *USP26* is exclusively expressed in testis (174). *USPs* are critical for cancer progression and several approaches to develop inhibitors of *USPs* for treatment of cancer are being pursued (175-177). It was shown that *USP26* promotes ESCC by stabilizing *SNAI1* (178).

miR-340 and *miR-365* [targeting phosphoserine aminotransferase 1 (*PSAT1*)]. Both these miRNAs were down-regulated in ESCC cell lines EC1, EC109, EC9706 and in ESCC tissues (179, 180). Both inhibited invasion of EC9706 and EC109 ESCCs (179, 180). *miR-340* as well as *miR-365* transfectants reduced growth of EC9706 xenografts in nude mice (179, 180). *miR-340* and *miR-365* inhibited EMT by up-regulation of E-cadherin, down-regulation of *SNAI1* and vimentin, and reduction of phosphorylated glycogen synthase kinase 3β (179, 180). *PSAT1*, involved in serine biosynthesis, is amplified in a significant subset of tumors and RNAi directed against *PSAT1* reduced cancer cell survival and growth; therefore, discovery of *PSAT1* inhibitors as anticancer agents is being pursued (181).

PSAT1 plays a crucial role in development of ESCC and its expression predicts poor survival (182).

miR-375 [targeting lactate dehydrogenase B and metadherin (*MTDH*)]. *miR-375* was down-regulated in ESCC clinical specimens in comparison to neighboring normal tissue sections, and a low level of *miR-375* was associated with poor prognosis (183). *miR-375* inhibited proliferation and migration of TE2 and T.Tn ESCCs (183). Lactate dehydrogenase B (*LDHB*) and *MTDH* were identified as direct targets of *miR-375* (183). A *miR-375*/atelocollagen complex administered subcutaneously suppressed growth of TE2 and T.Tn xenografts in nude mice (184). *miR-375* target *LDHB* converts lactose to pyruvate, which is further oxidized and is critical for mTOR-mediated tumorigenesis (185). *LDHB* also controls apoptosis and autophagy in tumor cells (186). The other *miR-375* target, *MTDH*, functions as a regulator of EMT in carcinomas (187). It plays a role in tumor progression, invasion, resistance to chemotherapy in many carcinomas including ESCC. *MTDH* is required for proliferation, migration and invasion of ESCC (188, 189).

miR-485-5p [targeting O-linked N-acetylglucosamine transferase (*OGT*)]. *miR-485-5p* was expressed at low levels in ESCC cell lines and inhibited cell proliferation, migration and invasion in TE-1 and ECA109 ESCCs (190). Tumor growth in nude mice was inhibited in TE-1 cells overexpressing *miR-485-5p* (190). *OGT* was identified as a direct target of *miR-485-5p* (190). *OGT* catalyzes addition of N-acetylglucosamine through O-glycosidic linkage to serine or threonine and an S-glycosidic linkage to cysteine (191, 192). *OGT* is aberrantly expressed in cancer and modifies signaling proteins, transcription factors, metabolic enzymes, histones and chromatin regulators (193).

miR-499 (targeting DNA polymerase β). DNA polymerase β has been identified as the target of *miR-499* in EC9706 and KYSE30 ESCCs (194). *miR-499* inhibited proliferation, induced apoptosis and reduced the DNA-repair capacity of EC9706 and KYSE30 ESCCs by targeting DNA polymerase β (194). *miR-499* also inhibited tumor growth of xenografts derived from these cell lines in nude mice (194). DNA polymerase β is essential for short-patch base excision repair. DNA polymerase β overexpression resulted in aneuploidy and tumorigenesis in nude immunodeficient mice (195, 196). Targeting DNA polymerase β is considered as an option for cancer therapy (197).

Additional Targets

In addition *miR-34a* and *miR-133b* should be mentioned. They target phospholipase epsilon 1 (*PLCE1*) (198) and squalene epoxidase (*SQE*) (199), respectively. *SQE* is a rate-limiting

enzyme in cholesterol biosynthesis (199). *In vivo* activity in ESCC-related preclinical xenografts was demonstrated with the corresponding targets, not with *miR-34a* and *miR-133b*.

Concluding Remarks

Up-regulated miRs indicate targets which have to be reconstituted with low-molecular-weight compounds or inhibited by miR antagonists such as locked nucleic acids and antagomirs (200). All antagonists are oligonucleotides with sequences complementary to endogenous miRs (200-203). Down-regulated miRs identify targets which can be inhibited by small molecules or antibody-related moieties, or which can be re-expressed by replacement therapy with miR mimetics or vector-based expression (200-203). miR mimetics are double-stranded RNAs which reconstitute the function of the corresponding miRs.

When deregulated miRs were grouped into categories as secreted factors and transmembrane receptors, transcription factors and metabolic enzymes, for secreted factors and transmembrane receptors, four miRs were up-regulated and 10 were down-regulated in ESCC tissues in comparison to matching normal tissues (Figure 1). VEGF (*miR-126*), EGFR (*miR-133b*), HER2 (*miR-193a*), IGF1R (*miR-375*) and CD47 (*133a*) seem to be the most promising targets for inhibition with small molecules and biological agents or reconstitution of the corresponding miRs.

In the category of transcription factors, we identified five miRs up-regulated and nine down-regulated with efficacy in preclinical *in vitro* and *in vivo* systems (Figure 2). Drugs targeting transcription factors such as estrogen receptor and androgen receptor are among the most impactful drugs in oncology (5). STAT3 (*miR-124*), SMAD4 (*miR-130-3p*), SOX4 (*miR-122a*), MYC (*miR-145*), ZEB1 (*miR-150*), FOXM1 (*miR-204*), NRF2 (*miR-507*), SLUG (*miR-630*) and PITX2 (*miR-664*) have emerged as potential targets for inhibition at the protein level or reconstitution of the corresponding miRs. A subset of ESCCs is addicted to NRF2 this aspect is worth further detailed investigation (156). In general, targeting transcription factors is associated with technical issues of tractability with respect to inhibition and specificity, as well as toxicity issues. Inhibitory efforts may target protein-protein interactions with co-factors, inhibition of transcription factor DNA binding, inhibition of expression of regulators of transcription factors, altering levels of ubiquitinylation and subsequent proteolysis (204-208). Proteolysis targeting chimeras are under active investigation, as well as cysteine reactive inhibitors, which target intrinsically disordered domains of transcription factors (204-208).

Six miRs targeting enzymes were down-regulated (Figure 3). TIGAR (*miR-144*), PSAT1 (*miR-340* and *miR-365*) and LDHB (*miR-375*) are metabolic enzymes. These targets and

their corresponding miRs deserve further validation for treatment of ESCC. Transformed cells adopt metabolism and support tumor initiation and progression and therefore become addicted to these changes (209-211). Drugs targeting metabolic enzymes such as the dihydrofolate reductase inhibitor methotrexate and thymidylate inhibitor 5-fluorouracil are well established in cancer therapy.

Inhibition of miRs and replacement therapy face several technical problems which are not discussed in this review. Among these issues are: delivery of the agents to tumor tissues, optimization of their escape after internalization, inappropriate biodistribution and optimization of their pharmacokinetic and pharmacodynamic properties (211-213). Further critical issues are off-site effects and cytokine-release syndrome (213). Recently the field has witnessed several drawbacks (214). However, cobomarsen, an oligonucleotide-based inhibitor of *miR-155*, was shown to slow growth of diffuse large cell B-cell lymphoma xenografts without any toxic effects and is currently being evaluated in several clinical studies in patients with hematological malignancies and seems to be well tolerated (215, 216). Nevertheless, clinical proof-of-concept of miR-based therapies is still pending.

Conflicts of Interest

AN is and UHW was an employee of Roche.

Authors' Contributions

AN and UHW jointly designed and prepared the article.

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Received November 23, 2021

Revised January 17, 2022

Accepted January 19, 2022