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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

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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 (TNFα)]. *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). TNFα 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 TNFα 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, G_1/G_2 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 disentegrin and metalloprotease with thrombospondin motifs 1 (ADAMTS1)]. *miR-548k* over-expression correlated with poor prognosis of patients with ESCC (35). *miR-548k* mediated proliferation and cell-cycle progression of KYSE30 and KYSE510 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 β4 (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*

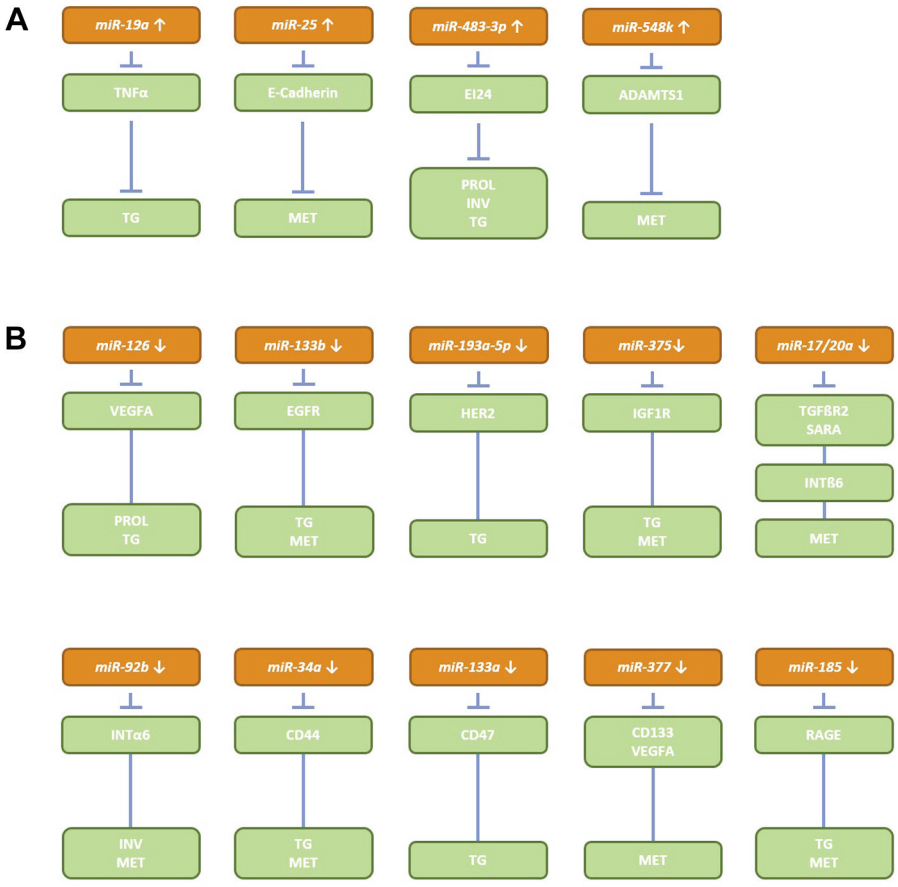

Figure 1. *Up-regulated (A) and down-regulated (B) miRs targeting secreted factors and transmembrane receptors in esophageal cancer cells in preclinical in vivo systems. ADAMTS1: A disintegin and metalloprotease with thrombospondin motifs 1; CD44, 47, 133: cluster of differentiation 44, 47, 133; EGFR: epidermal growth factor receptor; EI24: 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). *IGFR1* 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). *TGFRβ2* 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 TGFRβ2 at intracellular membranes (66). However, TGFβ 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 INTαv). *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). INTαv 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 18α and 8β 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 ESSC 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 de-glycosylated 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 forcancer 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

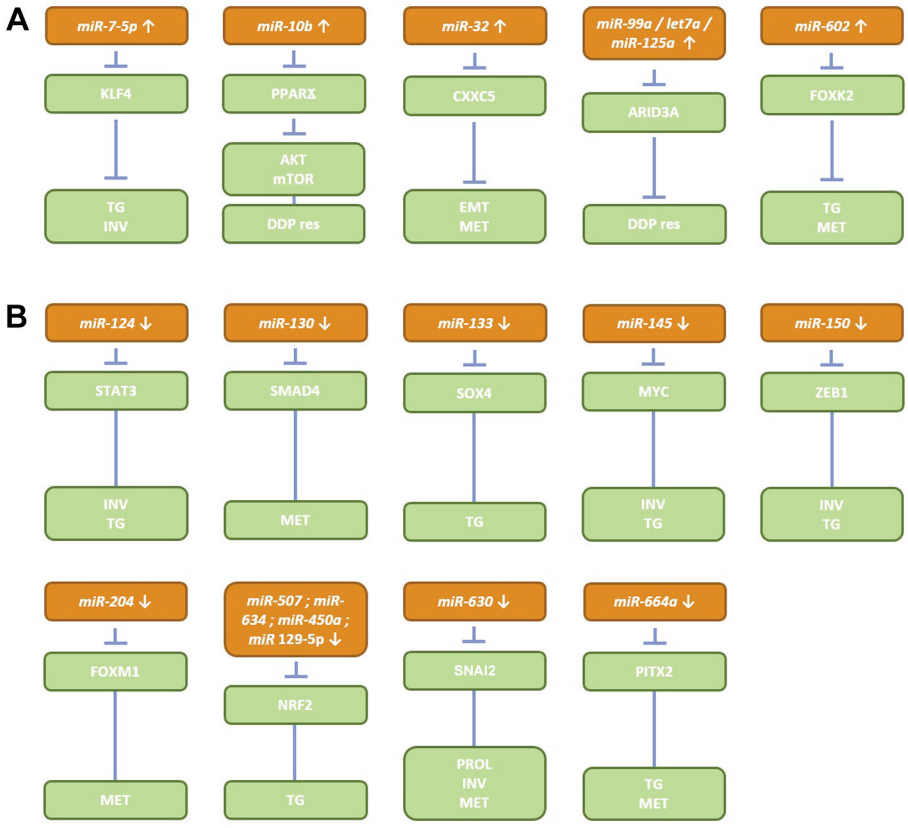

Figure 2. *Up-regulated (A) and down-regulated (B) miRs targeting transcription factors in esophageal cancer cells in preclinical in vivo systems. AKT: Serine-threonine kinase AKT; ARID3A: AT-rich interactive domain-containing protein 3A; CXX5: CCX-type zinc finger protein 5; DDP res: cisplatin resistance; EMT: epithelial–mesenchymal transition; FOXK2: forkhead box protein K2; FOXO31: forkhead-box protein 31; FOXM1: forkhead box protein M1; GSK3β: glycogen synthase kinase 3β; 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; PPARγ: 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 (PPARγ)]. miR-10b was up-regulated in patients with ESCC and targeted *PPARγ* (101). Suppression of *miR-10b* in ESCC cell lines enhanced chemosensitivity to cisplatin *in vitro* and *in vivo* (101). *PPARγ* enhanced resistance to cisplatin by activating AKT/mechanistic target of rapamycin (mTOR)/ribosomal protein70 S6 kinase (p70S6K) signaling (101). *PPARγ* 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 PPARγ ligands suppress proliferation and induce apoptosis of ESCCs by inhibiting toll-like receptor 4-dependent mitogen-activated protein kinase signaling (104). Reduced PPARγ 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 TGFβ signaling (106). CXXC5 inhibited WNT/βcatenin signaling, induced apoptosis by stimulating TGFβ/SMAD signaling and activated DNA repair *via* the serine-threonine kinase ataxic telangiectasia mutated/p53 pathway (107-109). In addition, CXXC5 promoted TGFβ 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 ESSC 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 TGFβ 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 TGFβ-induced EMT (128). In healthy and early-stage cancer cells, TGFβ 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 TGFβ signaling pathways (150). Silencing of *FOXM1* inhibited proliferation and migration of ESCCs (151). In ESCC, FOXM1 can activate phosphoinosite-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-ubiquitinylated 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 (SNAI2)]. Reduced *miR-630* expression was associated with poor survival in patients with ESCC (160, 161). Transcription factor *SNAI2*, 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*. SNAI2 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

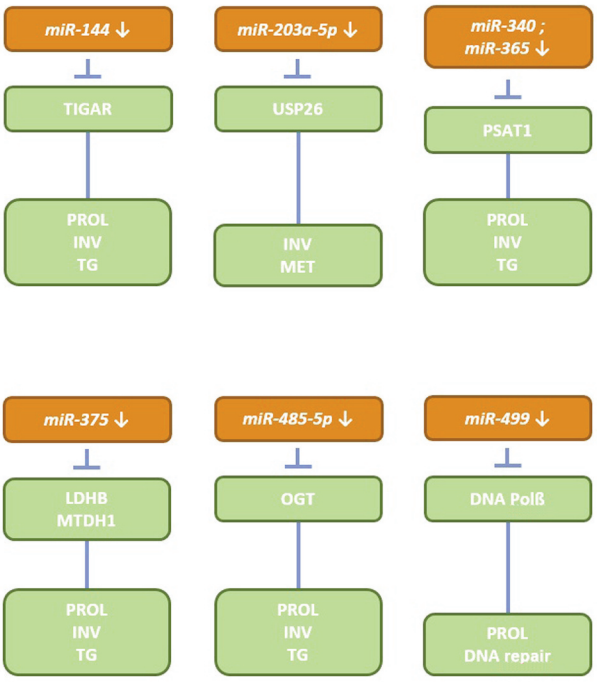

Figure 3. *Down-regulated miRs targeting enzymes in esophageal cancer cells mediating efficacy in preclinical in vivo systems DNA polβ: DNA polymerase β; LDHB: lactate dehydrogenase B; MET: metastasis; MTDH1: metadherin 1; OGT: O-linked-N-acetylglucosaminacetylation transferase; PROL: proliferation; 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 amino-transferase 1 (PSAT1)]. Both these miRs 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 pharmaco-kinetic and pharmaco-dynamic 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.

References

1 Hull R, Mbele M, Makhafola T, Hicks C, Wang SM, Reis RM, Mehrotra R, Mkhize-Kwitshana Z, Hussain S, Kibiki G, Bates DO and Dlamini Z: A multinational review: Oesophageal cancer in low to middle-income countries. Oncol Lett *20(4)*: 42, 2020. PMID: 32802164. DOI: 10.3892/ol.2020.11902

2 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2020. CA Cancer J Clin *70(1)*: 7-30, 2020. PMID: 31912902. DOI: 10.3322/caac.21590

3 Lordick F and Janjigian YY: Clinical impact of tumour biology in the management of gastroesophageal cancer. Nat Rev Clin Oncol *13(6)*: 348-360, 2016. PMID: 26925958. DOI: 10.1038/nrclinonc.2016.15

4 Testa U, Castelli G and Pelosi E: Esophageal cancer: Genomic and molecular characterization, stem cell compartment and clonal evolution. Medicines (Basel) *4(3)*: 67, 2017. PMID: 28930282. DOI: 10.3390/medicines4030067

5 Bujanda DE and Hachem C: Barrett's Esophagus. Mo Med *115(3)*: 211-213, 2018. PMID: 30228724.

6 Pusung M, Zeki S and Fitzgerald R: Genomics of esophageal cancer and biomarkers for early detection. Adv Exp Med Biol *908*: 237-263, 2016. PMID: 27573775. DOI: 10.1007/978-3-319-41388-4_12

7 Talukdar FR, di Pietro M, Secrier M, Moehler M, Goepfert K, Lima SSC, Pinto LFR, Hendricks D, Parker MI and Herceg Z: Molecular landscape of esophageal cancer: implications for early detection and personalized therapy. Ann NY Acad Sci *1434(1)*: 342-359, 2018. PMID: 29917250. DOI: 10.1111/nyas.13876

8 Baba Y, Nomoto D, Okadome K, Ishimoto T, Iwatsuki M, Miyamoto Y, Yoshida N and Baba H: Tumor immune microenvironment and immune checkpoint inhibitors in esophageal squamous cell carcinoma. Cancer Sci *111(9)*: 3132-3141, 2020. PMID: 32579769. DOI: 10.1111/cas.14541

9 Vivaldi C, Catanese S, Massa V, Pecora I, Salani F, Santi S, Lencioni M, Vasile E, Falcone A and Fornaro L: Immune checkpoint inhibitors in esophageal cancers: are we finally finding the right path in the mist? Int J Mol Sci *21(5)*: 1658, 2020. PMID: 32121290. DOI: 10.3390/ijms21051658

10 McGeary SE, Lin KS, Shi CY, Pham TM, Bisaria N, Kelley GM and Bartel DP: The biochemical basis of microRNA targeting efficacy. Science *366(6472)*: eaav1741, 2019. PMID: 31806698. DOI: 10.1126/science.aav1741

11 Garzon R, Calin GA and Croce CM: MicroRNAs in cancer. Annu Rev Med *60*: 167-179, 2009. PMID: 19630570. DOI: 10.1146/annurev.med.59.053006.104707

12 Lee YS and Dutta A: MicroRNAs in cancer. Annu Rev Pathol *4*: 199-227, 2009. PMID: 18817506. DOI: 10.1146/annurev.pathol.4.110807.092222

13 Weidle UH, Schmid D, Birzele F and Brinkmann U: MicroRNAs involved in metastasis of hepatocellular carcinoma: Target candidates, functionality and efficacy in animal models and prognostic relevance. Cancer Genomics Proteomics *17(1)*: 1-21, 2020. PMID: 31882547. DOI: 10.21873/cgp.20163

14 Weidle UH, Brinkmann U and Auslaender S: microRNAs and corresponding targets involved in metastasis of colorectal cancer in preclinical *in vivo* models. Cancer Genomics Proteomics *17(5)*: 453-468, 2020. PMID: 32859626. DOI: 10.21873/cgp.20204

15 Weidle UH, Birzele F and Nopora A: microRNAs promoting growth of gastric cancer xenografts and correlation to clinical prognosis. Cancer Genomics Proteomics *18(1)*: 1-15, 2021. PMID: 33419892. DOI: 10.21873/cgp.20237

16 Weidle UH and Nopora A: Identification of MicroRNAs with *in vivo* efficacy in multiple myeloma-related xenograft models. Cancer Genomics Proteomics *17(4)*: 321-334, 2020. PMID: 32576578. DOI: 10.21873/cgp.20192

17 Cimmino A, Calin GA, Fabbri M, Iorio MV, Ferracin M, Shimizu M, Wojcik SE, Aqeilan RI, Zupo S, Dono M, Rassenti L, Alder H, Volinia S, Liu CG, Kipps TJ, Negrini M and Croce CM: miR-15 and miR-16 induce apoptosis by targeting BCL2. Proc Natl Acad Sci USA *102(39)*: 13944-13949, 2005. PMID: 16166262. DOI: 10.1073/pnas.0506654102

18 Zhu H, Han C and Wu T: MiR-17-92 cluster promotes hepatocarcinogenesis. Carcinogenesis *36(10)*: 1213-1222, 2015. PMID: 26233958. DOI: 10.1093/carcin/bgv112

19 He B, Yin B, Wang B, Xia Z, Chen C and Tang J: MicroRNAs in esophageal cancer (review). Mol Med Rep *6(3)*: 459-465, 2012. PMID: 22751839. DOI: 10.3892/mmr.2012.975

20 Dias F, Morais M, Teixeira AL and Medeiros R: Involving the microRNA targetome in esophageal-cancer development and behavior. Cancers (Basel) *10(10)*: 381, 2018. PMID: 30322005. DOI: 10.3390/cancers10100381

21 Li X, Wainscott C and Xi Y: MicroRNA provides insight into understanding esophageal cancer. Thorac Cancer *2(4)*: 134-142, 2011. PMID: 27755846. DOI: 10.1111/j.1759-7714.2011.00059.x

22 Liu M, Wang Z, Yang S, Zhang W, He S, Hu C, Zhu H, Quan L, Bai J and Xu N: TNF-α is a novel target of miR-19a. Int J Oncol *38(4)*: 1013-1022, 2011. PMID: 21271217. DOI: 10.3892/ijo.2011.924

23 Wajant H: The role of TNF in cancer. Results Probl Cell Differ *49*: 1-15, 2009. PMID: 19137269. DOI: 10.1007/400_2008_26

24 Ham B, Fernandez MC, D'Costa Z and Brodt P: The diverse roles of the TNF axis in cancer progression and metastasis. Trends Cancer Res *11(1)*: 1-27, 2016. PMID: 27928197.

25 Balkwill F: TNF-alpha in promotion and progression of cancer. Cancer Metastasis Rev *25(3)*: 409-416, 2006. PMID: 16951987. DOI: 10.1007/s10555-006-9005-3

26 Josephs SF, Ichim TE, Prince SM, Kesari S, Marincola FM, Escobedo AR and Jafri A: Unleashing endogenous TNF-alpha as a cancer immunotherapeutic. J Transl Med *16(1)*: 242, 2018. PMID: 30170620. DOI: 10.1186/s12967-018-1611-7

27 Liu B, Li X, Li C, Xu R and Sun X: miR-25 mediates metastasis and epithelial-mesenchymal-transition in human esophageal squamous cell carcinoma *via* regulation of E-cadherin signaling. Bioengineered *10(1)*: 679-688, 2019. PMID: 31679450. DOI: 10.1080/21655979.2019.1687391

28 Cavallaro U and Christofori G: Cell adhesion and signalling by cadherins and Ig-CAMs in cancer. Nat Rev Cancer *4(2)*: 118-132, 2004. PMID: 14964308. DOI: 10.1038/nrc1276

29 Bruner HC and Derksen PWB: Loss of E-cadherin-dependent cell-cell adhesion and the development and progression of cancer. Cold Spring Harb Perspect Biol *10(3)*: a029330, 2018. PMID: 28507022. DOI: 10.1101/cshperspect.a029330

30 Li T, Xu L, Teng J, Ma Y, Liu W, Wang Y, Chi X, Shao S, Dong Y, Zhan Q and Liu X: GADD45G interacts with E-cadherin to suppress the migration and invasion of esophageal squamous cell carcinoma. Dig Dis Sci *65(4)*: 1032-1041, 2020. PMID: 31562612. DOI: 10.1007/s10620-019-05836-8

31 Ma J, Hong L, Xu G, Hao J, Wang R, Guo H, Liu J, Zhang Y, Nie Y and Fan D: miR-483-3p plays an oncogenic role in esophageal squamous cell carcinoma by targeting tumor suppressor EI24. Cell Biol Int *40(4)*: 448-455, 2016. PMID: 26801660. DOI: 10.1002/cbin.10585

32 Gu Z, Flemington C, Chittenden T and Zambetti GP: ei24, a p53 response gene involved in growth suppression and apoptosis. Mol Cell Biol *20(1)*: 233-241, 2000. PMID: 10594026. DOI: 10.1128/MCB.20.1.233-241.2000

33 Duan L, Ma J, Yang W, Cao L, Wang X, Niu L, Li Y, Zhou W, Zhang Y, Liu J, Zhang H, Zhao Q, Hong L and Fan D: EI24 inhibits cell proliferation and drug resistance of esophageal squamous cell carcinoma. Front Oncol *10*: 1570, 2020. PMID: 32974192. DOI: 10.3389/fonc.2020.01570

34 Choi JM, Devkota S, Sung YH and Lee HW: EI24 regulates epithelial-to-mesenchymal transition and tumor progression by suppressing TRAF2-mediated NF-κB activity. Oncotarget *4(12)*: 2383-2396, 2013. PMID: 24280371. DOI: 10.18632/oncotarget.1434

35 Zhang W, Hong R, Li L, Wang Y, Du P, Ou Y, Zhao Z, Liu X, Xiao W, Dong D, Wu Q, Chen J, Song Y and Zhan Q: The chromosome 11q13.3 amplification associated lymph node metastasis is driven by miR-548k through modulating tumor

microenvironment. Mol Cancer *17(1)*: 125, 2018. PMID: 30131072. DOI: 10.1186/s12943-018-0871-4

36 Mullooly M, McGowan PM, Crown J and Duffy MJ: The ADAMs family of proteases as targets for the treatment of cancer. Cancer Biol Ther *17(8)*: 870-880, 2016. PMID: 27115328. DOI: 10.1080/15384047.2016.1177684

37 Inagaki J, Takahashi K, Ogawa H, Asano K, Faruk Hatipoglu O, Cilek MZ, Obika M, Ohtsuki T, Hofmann M, Kusachi S, Ninomiya Y and Hirohata S: ADAMTS1 inhibits lymphangiogenesis by attenuating phosphorylation of the lymphatic endothelial cell-specific VEGF receptor. Exp Cell Res *323(2)*: 263-275, 2014. PMID: 24631293. DOI: 10.1016/j.yexcr.2014.03.002

38 Zheng W, Aspelund A and Alitalo K: Lymphangiogenic factors, mechanisms, and applications. J Clin Invest *124(3)*: 878-887, 2014. PMID: 24590272. DOI: 10.1172/JCI71603

39 Vaahtomeri K, Karaman S, Mäkinen T and Alitalo K: Lymphangiogenesis guidance by paracrine and pericellular factors. Genes Dev *31(16)*: 1615-1634, 2017. PMID: 28947496. DOI: 10.1101/gad.303776.117

40 Memon A and Lee WK: KLF10 as a tumor suppressor gene and its TGF-β signaling. Cancers (Basel) *10(6)*: 161, 2018. PMID: 29799499. DOI: 10.3390/cancers10060161

41 Kong R, Ma Y, Feng J, Li S, Zhang W, Jiang J, Zhang J, Qiao Z, Yang X and Zhou B: The crucial role of miR-126 on suppressing progression of esophageal cancer by targeting VEGF-A. Cell Mol Biol Lett *21*: 3, 2016. PMID: 28536606. DOI: 10.1186/s11658-016-0004-2

42 Apte RS, Chen DS and Ferrara N: VEGF in signaling and disease: Beyond discovery and development. Cell *176(6)*: 1248-1264, 2019. PMID: 30849371. DOI: 10.1016/j.cell.2019.01.021

43 Siveen KS, Prabhu K, Krishnankutty R, Kuttikrishnan S, Tsakou M, Alali FQ, Dermime S, Mohammad RM and Uddin S: Vascular endothelial growth factor (VEGF) signaling in tumour vascularization: Potential and challenges. Curr Vasc Pharmacol *15(4)*: 339-351, 2017. PMID: 28056756. DOI: 10.2174/1570161115666170105124038

44 Yang YM, Hong P, Xu WW, He QY and Li B: Advances in targeted therapy for esophageal cancer. Signal Transduct Target Ther *5(1)*: 229, 2020. PMID: 33028804. DOI: 10.1038/s41392-020-00323-3

45 Zhu JF, Liu Y, Huang H, Shan L, Han ZG, Liu JY, Li YL, Dong X and Zeng W: MicroRNA-133b/EGFR axis regulates esophageal squamous cell carcinoma metastases by suppressing anoikis resistance and anchorage-independent growth. Cancer Cell Int *18*: 193, 2018. PMID: 30479571. DOI: 10.1186/s12935-018-0684-y

46 Ciardiello F and Tortora G: EGFR antagonists in cancer treatment. N Engl J Med *358(11)*: 1160-1174, 2008. PMID: 18337605. DOI: 10.1056/NEJMra0707704

47 Guardiola S, Varese M, Sánchez-Navarro M and Giralt E: A third shot at EGFR: New opportunities in cancer therapy. Trends Pharmacol Sci *40(12)*: 941-955, 2019. PMID: 31706618. DOI: 10.1016/j.tips.2019.10.004

48 Hong L, Han Y and Brain L: Epidermal growth factor receptor: an important target in esophageal cancer. Expert Opin Ther Targets *17(10)*: 1179-1185, 2013. PMID: 23855932. DOI: 10.1517/14728222.2013.820709

49 Itakura Y, Sasano H, Shiga C, Furukawa Y, Shiga K, Mori S and Nagura H: Epidermal growth factor receptor overexpression in esophageal carcinoma. An immunohistochemical study correlated with clinicopathologic findings and DNA amplification. Cancer *74(3)*: 795-804, 1994. PMID: 8039107. DOI: 10.1002/1097-0142(19940801)74:3<795::aid-cncr2820740303>3.0.co;2-i

50 Kitagawa Y, Ueda M, Ando N, Ozawa S, Shimizu N and Kitajima M: Further evidence for prognostic significance of epidermal growth factor receptor gene amplification in patients with esophageal squamous cell carcinoma. Clin Cancer Res *2(5)*: 909-914, 1996. PMID: 9816249.

51 Lin CH, Tsai CH, Yeh CT, Liang JL, Hung WC, Lin FC, Chang WL, Li HY, Yao YC, Hsu TI, Lee YC, Wang YC, Sheu BS, Lai WW, Calkins MJ, Hsiao M and Lu PJ: MiR-193a-5p/ERBB2 act as concurrent chemoradiation therapy response indicator of esophageal squamous cell carcinoma. Oncotarget *7(26)*: 39680-39693, 2016. PMID: 27203740. DOI: 10.18632/oncotarget.9444

52 Gros SJ, Kurschat N, Dohrmann T, Reichelt U, Dancau AM, Peldschus K, Adam G, Hoffman RM, Izbicki JR and Kaifi JT: Effective therapeutic targeting of the overexpressed HER-2 receptor in a highly metastatic orthotopic model of esophageal carcinoma. Mol Cancer Ther *9(7)*: 2037-2045, 2010. PMID: 20606043. DOI: 10.1158/1535-7163.MCT-10-0209

53 Kato H, Arao T, Matsumoto K, Fujita Y, Kimura H, Hayashi H, Nishiki K, Iwama M, Shiraishi O, Yasuda A, Shinkai M, Imano M, Imamoto H, Yasuda T, Okuno K, Shiozaki H and Nishio K: Gene amplification of EGFR, HER2, FGFR2 and MET in esophageal squamous cell carcinoma. Int J Oncol *42(4)*: 1151-1158, 2013. PMID: 23426935. DOI: 10.3892/ijo.2013.1830

54 Gonzaga IM, Soares-Lima SC, de Santos PT, Blanco TC, de Reis BS, Quintella DC, de Oliveira IM, de Faria PA, Kruel CD, Andreollo NA, de Simão TA and Pinto LF: Alterations in epidermal growth factor receptors 1 and 2 in esophageal squamous cell carcinomas. BMC Cancer *12*: 569, 2012. PMID: 23207070. DOI: 10.1186/1471-2407-12-569

55 Schoppmann SF, Jesch B, Friedrich J, Wrba F, Schultheis A, Pluschnig U, Maresch J, Zacherl J, Hejna M and Birner P: Expression of Her-2 in carcinomas of the esophagus. Am J Surg Pathol *34(12)*: 1868-1873, 2010. PMID: 21107094. DOI: 10.1097/PAS.0b013e3181f8be17

56 Fichter CD, Timme S, Braun JA, Gudernatsch V, Schöpflin A, Bogatyreva L, Geddert H, Faller G, Klimstra D, Tang L, Hauschke D, Werner M and Lassmann S: EGFR, HER2 and HER3 dimerization patterns guide targeted inhibition in two histotypes of esophageal cancer. Int J Cancer *135(7)*: 1517-1530, 2014. PMID: 24510732. DOI: 10.1002/ijc.28771

57 Kong KL, Kwong DL, Chan TH, Law SY, Chen L, Li Y, Qin YR and Guan XY: MicroRNA-375 inhibits tumour growth and metastasis in oesophageal squamous cell carcinoma through repressing insulin-like growth factor 1 receptor. Gut *61(1)*: 33-42, 2012. PMID: 21813472. DOI: 10.1136/gutjnl-2011-300178

58 Zha J and Lackner MR: Targeting the insulin-like growth factor receptor-1R pathway for cancer therapy. Clin Cancer Res *16(9)*: 2512-2517, 2010. PMID: 20388853. DOI: 10.1158/1078-0432.CCR-09-2232

59 Ouban A, Muraca P, Yeatman T and Coppola D: Expression and distribution of insulin-like growth factor-1 receptor in human carcinomas. Hum Pathol *34(8)*: 803-808, 2003. PMID: 14506643. DOI: 10.1016/s0046-8177(03)00291-0

60 Liu YC, Leu CM, Wong FH, Fong WS, Chen SC, Chang C and Hu CP: Autocrine stimulation by insulin-like growth factor I is involved in the growth, tumorigenicity and chemoresistance of human esophageal carcinoma cells. J Biomed Sci *9(6 Pt 2)*: 665-674, 2002. PMID: 12432233. DOI: 10.1159/000067282

61 Imsumran A, Adachi Y, Yamamoto H, Li R, Wang Y, Min Y, Piao W, Nosho K, Arimura Y, Shinomura Y, Hosokawa M, Lee CT, Carbone DP and Imai K: Insulin-like growth factor-I receptor as a marker for prognosis and a therapeutic target in human esophageal squamous cell carcinoma. Carcinogenesis *28(5)*: 947-956, 2007. PMID: 17183068. DOI: 10.1093/carcin/bgl247

62 Doyle SL, Donohoe CL, Finn SP, Howard JM, Lithander FE, Reynolds JV, Pidgeon GP and Lysaght J: IGF-1 and its receptor in esophageal cancer: association with adenocarcinoma and visceral obesity. Am J Gastroenterol *107(2)*: 196-204, 2012. PMID: 22146489. DOI: 10.1038/ajg.2011.417

63 Zhang T, Shen H, Dong W, Qu X, Liu Q and Du J: Antitumor effects and molecular mechanisms of figitumumab, a humanized monoclonal antibody to IGF-1 receptor, in esophageal carcinoma. Sci Rep *4*: 6855, 2014. PMID: 25358597. DOI: 10.1038/srep06855

64 Jing C, Ma G, Li X, Wu X, Huang F, Liu K and Liu Z: MicroRNA-17/20a impedes migration and invasion *via* TGF-β/ITGB6 pathway in esophageal squamous cell carcinoma. Am J Cancer Res *6(7)*: 1549-1562, 2016. PMID: 27508097.

65 Shi Y and Massagué J: Mechanisms of TGF-beta signaling from cell membrane to the nucleus. Cell *113(6)*: 685-700, 2003. PMID: 12809600. DOI: 10.1016/s0092-8674(03)00432-x

66 Chen YG: Endocytic regulation of TGF-beta signaling. Cell Res *19(1)*: 58-70, 2009. PMID: 19050695. DOI: 10.1038/cr.2008.315

67 Massagué J: TGFbeta in cancer. Cell *134(2)*: 215-230, 2008. PMID: 18662538. DOI: 10.1016/j.cell.2008.07.001

68 Massagué J: TGFβ signalling in context. Nat Rev Mol Cell Biol *13(10)*: 616-630, 2012. PMID: 22992590. DOI: 10.1038/nrm3434

69 Ma G, Jing C, Li L, Huang F, Ding F, Wang B, Lin D, Luo A and Liu Z: MicroRNA-92b represses invasion-metastasis cascade of esophageal squamous cell carcinoma. Oncotarget *7(15)*: 20209-20222, 2016. PMID: 26934001. DOI: 10.18632/oncotarget.7747

70 Sulzmaier FJ, Jean C and Schlaepfer DD: FAK in cancer: mechanistic findings and clinical applications. Nat Rev Cancer *14(9)*: 598-610, 2014. PMID: 25098269. DOI: 10.1038/nrc3792

71 Hynes RO: Integrins: bidirectional, allosteric signaling machines. Cell *110(6)*: 673-687, 2002. PMID: 12297042. DOI: 10.1016/s0092-8674(02)00971-6

72 Guo W and Giancotti FG: Integrin signalling during tumour progression. Nat Rev Mol Cell Biol *5(10)*: 816-826, 2004. PMID: 15459662. DOI: 10.1038/nrm1490

73 Zuo J, Zhu K, Wang Y and Yu Z: MicroRNA-34a suppresses invasion and metastatic in esophageal squamous cell carcinoma by regulating CD44. Mol Cell Biochem *443(1-2)*: 139-149, 2018. PMID: 29094237. DOI: 10.1007/s11010-017-3218-3

74 Ponta H, Sherman L and Herrlich PA: CD44: from adhesion molecules to signalling regulators. Nat Rev Mol Cell Biol *4(1)*: 33-45, 2003. PMID: 12511867. DOI: 10.1038/nrm1004

75 Chen C, Zhao S, Karnad A and Freeman JW: The biology and role of CD44 in cancer progression: therapeutic implications. J Hematol Oncol *11(1)*: 64, 2018. PMID: 29747682. DOI: 10.1186/s13045-018-0605-5

76 Goodison S, Urquidi V and Tarin D: CD44 cell adhesion molecules. Mol Pathol *52(4)*: 189-196, 1999. PMID: 10694938. DOI: 10.1136/mp.52.4.189

77 Weidle UH, Maisel D, Klostermann S, Weiss EH and Schmitt M: Differential splicing generates new transmembrane receptor and extracellular matrix-related targets for antibody-based therapy of cancer. Cancer Genomics Proteomics *8(5)*: 211-226, 2011. PMID: 21980036.

78 Le Bras GF, Allison GL, Richards NF, Ansari SS, Washington MK and Andl CD: CD44 upregulation in E-cadherin-negative esophageal cancers results in cell invasion. PLoS One *6(11)*: e27063, 2011. PMID: 22069487. DOI: 10.1371/journal.pone.0027063

79 Zhao JS, Li WJ, Ge D, Zhang PJ, Li JJ, Lu CL, Ji XD, Guan DX, Gao H, Xu LY, Li EM, Soukiasian H, Koeffler HP, Wang XF and Xie D: Tumor initiating cells in esophageal squamous cell carcinomas express high levels of CD44. PLoS One *6(6)*: e21419, 2011. PMID: 21731740. DOI: 10.1371/journal.pone.0021419

80 Kamil Mohammed Al-Mosawi A, Cheshomi H, Hosseinzadeh A and M Matin M: Prognostic and clinical value of CD44 and CD133 in esophageal cancer: a systematic review and meta-analysis. Iran J Allergy Asthma Immunol *19(2)*: 105-116, 2020. PMID: 32372624. DOI: 10.18502/ijaai.v19i2.2756

81 Suzuki S, Yokobori T, Tanaka N, Sakai M, Sano A, Inose T, Sohda M, Nakajima M, Miyazaki T, Kato H and Kuwano H: CD47 expression regulated by the miR-133a tumor suppressor is a novel prognostic marker in esophageal squamous cell carcinoma. Oncol Rep *28(2)*: 465-472, 2012. PMID: 22641236. DOI: 10.3892/or.2012.1831

82 Feng M, Jiang W, Kim BYS, Zhang CC, Fu YX and Weissman IL: Phagocytosis checkpoints as new targets for cancer immunotherapy. Nat Rev Cancer *19(10)*: 568-586, 2019. PMID: 31462760. DOI: 10.1038/s41568-019-0183-z

83 Chao MP, Takimoto CH, Feng DD, McKenna K, Gip P, Liu J, Volkmer JP, Weissman IL and Majeti R: Therapeutic targeting of the macrophage immune checkpoint CD47 in myeloid malignancies. Front Oncol *9*: 1380, 2020. PMID: 32038992. DOI: 10.3389/fonc.2019.01380

84 Murata Y, Saito Y, Kotani T and Matozaki T: CD47-signal regulatory protein α signaling system and its application to cancer immunotherapy. Cancer Sci *109(8)*: 2349-2357, 2018. PMID: 29873856. DOI: 10.1111/cas.13663

85 Zhao CL, Yu S, Wang SH, Li SG, Wang ZJ and Han SN: Characterization of cluster of differentiation 47 expression and its potential as a therapeutic target in esophageal squamous cell cancer. Oncol Lett *15(2)*: 2017-2023, 2018. PMID: 29399202. DOI: 10.3892/ol.2017.7447

86 Li B, Xu WW, Han L, Chan KT, Tsao SW, Lee NPY, Law S, Xu LY, Li EM, Chan KW, Qin YR, Guan XY, He QY and Cheung ALM: MicroRNA-377 suppresses initiation and progression of esophageal cancer by inhibiting CD133 and VEGF. Oncogene *36(28)*: 3986-4000, 2017. PMID: 28288140. DOI: 10.1038/onc.2017.29

87 Glumac PM and LeBeau AM: The role of CD133 in cancer: a concise review. Clin Transl Med *7(1)*: 18, 2018. PMID: 29984391. DOI: 10.1186/s40169-018-0198-1

88 Valent P, Bonnet D, De Maria R, Lapidot T, Copland M, Melo JV, Chomienne C, Ishikawa F, Schuringa JJ, Stassi G, Huntly B, Herrmann H, Soulier J, Roesch A, Schuurhuis GJ, Wöhrer S, Arock M, Zuber J, Cerny-Reiterer S, Johnsen HE, Andreeff M and Eaves C: Cancer stem cell definitions and terminology: the devil is in the details. Nat Rev Cancer *12(11)*: 767-775, 2012. PMID: 23051844. DOI: 10.1038/nrc3368

89 Liou GY: CD133 as a regulator of cancer metastasis through the cancer stem cells. Int J Biochem Cell Biol *106*: 1-7, 2019. PMID: 30399449. DOI: 10.1016/j.biocel.2018.10.013

90 Xu WW, Li B, Zhao JF, Yang JG, Li JQ, Tsao SW, He QY and Cheung ALM: IGF2 induces CD133 expression in esophageal

cancer cells to promote cancer stemness. Cancer Lett *425*: 88-100, 2018. PMID: 29604392. DOI: 10.1016/j.canlet.2018.03.039

91 Sui YP, Jian XP, Ma LI, Xu GZ, Liao HW, Liu YP and Wen HC: Prognostic value of cancer stem cell marker CD133 expression in esophageal carcinoma: A meta-analysis. Mol Clin Oncol *4(1)*: 77-82, 2016. PMID: 26870362. DOI: 10.3892/mco.2015.651

92 Jing R, Chen W, Wang H, Ju S, Cong H, Sun B, Jin Q, Chu S, Xu L and Cui M: Plasma miR-185 is decreased in patients with esophageal squamous cell carcinoma and might suppress tumor migration and invasion by targeting RAGE. Am J Physiol Gastrointest Liver Physiol *309(9)*: G719-G729, 2015. PMID: 26316588. DOI: 10.1152/ajpgi.00078.2015

93 Palanissami G and Paul SFD: RAGE and its ligands: Molecular interplay between glycation, inflammation, and hallmarks of cancer-a review. Horm Cancer *9(5)*: 295-325, 2018. PMID: 29987748. DOI: 10.1007/s12672-018-0342-9

94 Jangde N, Ray R and Rai V: RAGE and its ligands: from pathogenesis to therapeutics. Crit Rev Biochem Mol Biol *55(6)*: 555-575, 2020. PMID: 32933340. DOI: 10.1080/10409238.2020.1819194

95 Tateno T, Ueno S, Hiwatashi K, Matsumoto M, Okumura H, Setoyama T, Uchikado Y, Sakoda M, Kubo F, Ishigami S, Shinchi H and Natsugoe S: Expression of receptor for advanced glycation end products (RAGE) is related to prognosis in patients with esophageal squamous cell carcinoma. Ann Surg Oncol *16(2)*: 440-446, 2009. PMID: 19023628. DOI: 10.1245/s10434-008-0237-z

96 Shi W, Song J, Gao Z, Liu X and Wang W: Downregulation of miR-7-5p inhibits the tumorigenesis of esophagus cancer *via* targeting KLF4. Onco Targets Ther *13*: 9443-9453, 2020. PMID: 33061430. DOI: 10.2147/OTT.S251508

97 Ghaleb AM and Yang VW: Krüppel-like factor 4 (KLF4): What we currently know. Gene *611*: 27-37, 2017. PMID: 28237823. DOI: 10.1016/j.gene.2017.02.025

98 Taracha-Wisniewska A, Kotarba G, Dworkin S and Wilanowski T: Recent discoveries on the involvement of Krüppel-like factor 4 in the most common cancer types. Int J Mol Sci *21(22)*: 8843, 2020. PMID: 33266506. DOI: 10.3390/ijms21228843

99 He H, Li S, Hong Y, Zou H, Chen H, Ding F, Wan Y and Liu Z: Krüppel-like factor 4 promotes esophageal squamous cell carcinoma differentiation by up-regulating Keratin 13 expression. J Biol Chem *290(21)*: 13567-13577, 2015. PMID: 25851906. DOI: 10.1074/jbc.M114.629717

100 Ma MQ, Zhang HD, Tang P, Jiang HJ and Chen CG: Association of Kruppel-like factor 4 expression with the prognosis of esophageal squamous cell carcinoma patients. Int J Clin Exp Pathol *7(10)*: 6679-6685, 2014. PMID: 25400747.

101 Wu K, Hu Y, Yan K, Qi Y, Zhang C, Zhu D, Liu D and Zhao S: microRNA-10b confers cisplatin resistance by activating AKT/mTOR/P70S6K signaling *via* targeting PPARγ in esophageal cancer. J Cell Physiol *235(2)*: 1247-1258, 2020. PMID: 31267531. DOI: 10.1002/jcp.29040

102 Mirza AZ, Althagafi II and Shamshad H: Role of PPAR receptor in different diseases and their ligands: Physiological importance and clinical implications. Eur J Med Chem *166*: 502-513, 2019. PMID: 30739829. DOI: 10.1016/j.ejmech.2019.01.067

103 Yousefnia S, Momenzadeh S, Seyed Forootan F, Ghaedi K and Nasr Esfahani MH: The influence of peroxisome proliferator-activated receptor γ (PPARγ) ligands on cancer cell tumorigenicity. Gene *649*: 14-22, 2018. PMID: 29369787. DOI: 10.1016/j.gene.2018.01.018

104 Wu K, Yang Y, Liu D, Qi Y, Zhang C, Zhao J and Zhao S: Activation of PPARγ suppresses proliferation and induces apoptosis of esophageal cancer cells by inhibiting TLR4-dependent MAPK pathway. Oncotarget *7(28)*: 44572-44582, 2016. PMID: 27323819. DOI: 10.18632/oncotarget.10067

105 Terashita Y, Sasaki H, Haruki N, Nishiwaki T, Ishiguro H, Shibata Y, Kudo J, Konishi S, Kato J, Koyama H, Kimura M, Sato A, Shinoda N, Kuwabara Y and Fujii Y: Decreased peroxisome proliferator-activated receptor gamma gene expression is correlated with poor prognosis in patients with esophageal cancer. Jpn J Clin Oncol *32(7)*: 238-243, 2002. PMID: 12324573. DOI: 10.1093/jjco/hyf056

106 Liu YT, Zong D, Jiang XS, Yin L, Wang LJ, Wang TT, Zhu J and He X: miR-32 promotes esophageal squamous cell carcinoma metastasis by targeting CXXC5. J Cell Biochem *120(4)*: 6250-6263, 2019. PMID: 30362164. DOI: 10.1002/jcb.27912

107 Xiong X, Tu S, Wang J, Luo S and Yan X: CXXC5: A novel regulator and coordinator of TGF-β, BMP and Wnt signaling. J Cell Mol Med *23(2)*: 740-749, 2019. PMID: 30479059. DOI: 10.1111/jcmm.14046

108 Andersson T, Södersten E, Duckworth JK, Cascante A, Fritz N, Sacchetti P, Cervenka I, Bryja V and Hermanson O: CXXC5 is a novel BMP4-regulated modulator of Wnt signaling in neural stem cells. J Biol Chem *284(6)*: 3672-3681, 2009. PMID: 19001364. DOI: 10.1074/jbc.M808119200

109 Zhang M, Wang R, Wang Y, Diao F, Lu F, Gao D, Chen D, Zhai Z and Shu H: The CXXC finger 5 protein is required for DNA damage-induced p53 activation. Sci China C Life Sci *52(6)*: 528-538, 2009. PMID: 19557330. DOI: 10.1007/s11427-009-0083-7

110 Yan X, Wu J, Jiang Q, Cheng H, Han JJ and Chen YG: CXXC5 suppresses hepatocellular carcinoma by promoting TGF-β-induced cell cycle arrest and apoptosis. J Mol Cell Biol *10(1)*: 48-59, 2018. PMID: 29036306. DOI: 10.1093/jmcb/mjx042

111 Ma J, Zhan Y, Xu Z, Li Y, Luo A, Ding F, Cao X, Chen H and Liu Z: ZEB1 induced miR-99b/let-7e/miR-125a cluster promotes invasion and metastasis in esophageal squamous cell carcinoma. Cancer Lett *398*: 37-45, 2017. PMID: 28408353. DOI: 10.1016/j.canlet.2017.04.006

112 Kurkewich JL, Klopfenstein N, Hallas WM, Wood C, Sattler RA, Das C, Tucker H, Dahl R and Cowden Dahl KD: Arid3b is critical for B lymphocyte development. PLoS One *11(8)*: e0161468, 2016. PMID: 27537840. DOI: 10.1371/journal.pone.0161468

113 Samyesudhas SJ, Roy L and Cowden Dahl KD: Differential expression of ARID3B in normal adult tissue and carcinomas. Gene *543(1)*: 174-180, 2014. PMID: 24704276. DOI: 10.1016/j.gene.2014.04.007

114 Zhang Y, Xu Y, Li Z, Zhu Y, Wen S, Wang M, Lv H, Zhang F and Tian Z: Identification of the key transcription factors in esophageal squamous cell carcinoma. J Thorac Dis *10(1)*: 148-161, 2018. PMID: 29600044. DOI: 10.21037/jtd.2017.12.27

115 Liu M, Yu J, Wang D, Niu Y, Chen S, Gao P, Yang Z, Wang H, Zhang J, Zhang C, Zhao Y, Hu W and Sun G: Epigenetically upregulated MicroRNA-602 is involved in a negative feedback loop with FOXK2 in esophageal squamous cell carcinoma. Mol Ther *27(10)*: 1796-1809, 2019. PMID: 31401147. DOI: 10.1016/j.ymthe.2019.07.006

116 Nestal de Moraes G, Carneiro LDT, Maia RC, Lam EW and Sharrocks AD: FOXK2 transcription factor and its emerging roles in cancer. Cancers (Basel) *11(3)*: 393, 2019. PMID: 30897782. DOI: 10.3390/cancers11030393

117 Liu Y, Ding W, Ge H, Ponnusamy M, Wang Q, Hao X, Wu W, Zhang Y, Yu W, Ao X and Wang J: FOXK transcription factors: Regulation and critical role in cancer. Cancer Lett *458*: 1-12, 2019. PMID: 31132431. DOI: 10.1016/j.canlet.2019.05.030

118 Liu X, Wei X, Niu W, Wang D, Wang B and Zhuang H: Downregulation of FOXK2 is associated with poor prognosis in patients with gastric cancer. Mol Med Rep *18(5)*: 4356-4364, 2018. PMID: 30221666. DOI: 10.3892/mmr.2018.9466

119 Cheng Y, Li Y, Nian Y, Liu D, Dai F and Zhang J: STAT3 is involved in miR-124-mediated suppressive effects on esophageal cancer cells. BMC Cancer *15*: 306, 2015. PMID: 25928665. DOI: 10.1186/s12885-015-1303-0

120 Furtek SL, Backos DS, Matheson CJ and Reigan P: Strategies and approaches of targeting STAT3 for cancer treatment. ACS Chem Biol *11(2)*: 308-318, 2016. PMID: 26730496. DOI: 10.1021/acschembio.5b00945

121 Yu H, Lee H, Herrmann A, Buettner R and Jove R: Revisiting STAT3 signalling in cancer: new and unexpected biological functions. Nat Rev Cancer *14(11)*: 736-746, 2014. PMID: 25342631. DOI: 10.1038/nrc3818

122 Lee H, Jeong AJ and Ye SK: Highlighted STAT3 as a potential drug target for cancer therapy. BMB Rep *52(7)*: 415-423, 2019. PMID: 31186087.

123 Hemmann U, Gerhartz C, Heesel B, Sasse J, Kurapkat G, Grötzinger J, Wollmer A, Zhong Z, Darnell JE Jr, Graeve L, Heinrich PC and Horn F: Differential activation of acute phase response factor/Stat3 and Stat1 *via* the cytoplasmic domain of the interleukin 6 signal transducer gp130. II. Src homology SH2 domains define the specificity of stat factor activation. J Biol Chem *271(22)*: 12999-13007, 1996. PMID: 8662795. DOI: 10.1074/jbc.271.22.12999

124 Wang Z, Zhu S, Shen M, Liu J, Wang M, Li C, Wang Y, Deng A and Mei Q: STAT3 is involved in esophageal carcinogenesis through regulation of Oct-1. Carcinogenesis *34(3)*: 678-688, 2013. PMID: 23172665. DOI: 10.1093/carcin/bgs361

125 Timme S, Ihde S, Fichter CD, Waehle V, Bogatyreva L, Atanasov K, Kohler I, Schöpflin A, Geddert H, Faller G, Klimstra D, Tang L, Reinheckel T, Hauschke D, Busch H, Boerries M, Werner M and Lassmann S: STAT3 expression, activity and functional consequences of STAT3 inhibition in esophageal squamous cell carcinomas and Barrett's adenocarcinomas. Oncogene *33(25)*: 3256-3266, 2014. PMID: 23912451. DOI: 10.1038/onc.2013.298

126 Tian X, Fei Q, Du M, Zhu H, Ye J, Qian L, Lu Z, Zhang W, Wang Y, Peng F, Chen J, Liu B, Li Q, He X and Yin L: miR-130a-3p regulated TGF-β1-induced epithelial-mesenchymal transition depends on SMAD4 in EC-1 cells. Cancer Med *8(3)*: 1197-1208, 2019. PMID: 30741461. DOI: 10.1002/cam4.1981

127 Zhao M, Mishra L and Deng CX: The role of TGF-β/SMAD4 signaling in cancer. Int J Biol Sci *14(2)*: 111-123, 2018. PMID: 29483830. DOI: 10.7150/ijbs.23230

128 Deckers M, van Dinther M, Buijs J, Que I, Löwik C, van der Pluijm G and ten Dijke P: The tumor suppressor Smad4 is required for transforming growth factor beta-induced epithelial to mesenchymal transition and bone metastasis of breast cancer cells. Cancer Res *66(4)*: 2202-2209, 2006. PMID: 16489022. DOI: 10.1158/0008-5472.CAN-05-3560

129 Colak S and Ten Dijke P: Targeting TGF-β signaling in cancer. Trends Cancer *3(1)*: 56-71, 2017. PMID: 28718426. DOI: 10.1016/j.trecan.2016.11.008

130 Syed V: TGF-β signaling in cancer. J Cell Biochem *117(6)*: 1279-1287, 2016. PMID: 26774024. DOI: 10.1002/jcb.25496

131 Li S, Qin X, Li Y, Zhang X, Niu R, Zhang H, Cui A, An W and Wang X: MiR-133a suppresses the migration and invasion of esophageal cancer cells by targeting the EMT regulator SOX4. Am J Transl Res *7(8)*: 1390-1403, 2015. PMID: 26396670.

132 Penzo-Méndez AI: Critical roles for SoxC transcription factors in development and cancer. Int J Biochem Cell Biol *42(3)*: 425-428, 2010. PMID: 19651233. DOI: 10.1016/j.biocel.2009.07.018

133 Lee AK, Ahn SG, Yoon JH and Kim SA: Sox4 stimulates ß-catenin activity through induction of CK2. Oncol Rep *25(2)*: 559-565, 2011. PMID: 21165564. DOI: 10.3892/or.2010.1091

134 Tiwari N, Tiwari VK, Waldmeier L, Balwierz PJ, Arnold P, Pachkov M, Meyer-Schaller N, Schübeler D, van Nimwegen E and Christofori G: Sox4 is a master regulator of epithelial-mesenchymal transition by controlling Ezh2 expression and epigenetic reprogramming. Cancer Cell *23(6)*: 768-783, 2013. PMID: 23764001. DOI: 10.1016/j.ccr.2013.04.020

135 Vervoort SJ, Lourenço AR, van Boxtel R and Coffer PJ: SOX4 mediates TGF-β-induced expression of mesenchymal markers during mammary cell epithelial to mesenchymal transition. PLoS One *8(1)*: e53238, 2013. PMID: 23301048. DOI: 10.1371/journal.pone.0053238

136 Wang F, Xia J, Wang N and Zong H: miR-145 inhibits proliferation and invasion of esophageal squamous cell carcinoma in part by targeting c-Myc. Onkologie *36(12)*: 754-758, 2013. PMID: 24356567. DOI: 10.1159/000356978

137 Schuhmacher M, Kohlhuber F, Hölzel M, Kaiser C, Burtscher H, Jarsch M, Bornkamm GW, Laux G, Polack A, Weidle UH and Eick D: The transcriptional program of a human B cell line in response to Myc. Nucleic Acids Res *29(2)*: 397-406, 2001. PMID: 11139609. DOI: 10.1093/nar/29.2.397

138 Schuhmacher M, Staege MS, Pajic A, Polack A, Weidle UH, Bornkamm GW, Eick D and Kohlhuber F: Control of cell growth by c-Myc in the absence of cell division. Curr Biol *9(21)*: 1255-1258, 1999. PMID: 10556095. DOI: 10.1016/s0960-9822(99)80507-7

139 Schlosser I, Hölzel M, Mürnseer M, Burtscher H, Weidle UH and Eick D: A role for c-Myc in the regulation of ribosomal RNA processing. Nucleic Acids Res *31(21)*: 6148-6156, 2003. PMID: 14576301. DOI: 10.1093/nar/gkg794

140 Wang J, Liu Z, Wang Z, Wang S, Chen Z, Li Z, Zhang M, Zou J, Dong B, Gao J and Shen L: Targeting c-Myc: JQ1 as a promising option for c-Myc-amplified esophageal squamous cell carcinoma. Cancer Lett *419*: 64-74, 2018. PMID: 29366803. DOI: 10.1016/j.canlet.2018.01.051

141 Lian Y, Niu X, Cai H, Yang X, Ma H, Ma S, Zhang Y and Chen Y: Clinicopathological significance of c-MYC in esophageal squamous cell carcinoma. Tumour Biol *39(7)*: 1010428317715804, 2017. PMID: 28671049. DOI: 10.1177/1010428317715804

142 Villanueva MT: Long path to MYC inhibition approaches clinical trials. Nat Rev Cancer *19(5)*: 252, 2019. PMID: 30967650. DOI: 10.1038/s41568-019-0141-9

143 Yokobori T, Suzuki S, Tanaka N, Inose T, Sohda M, Sano A, Sakai M, Nakajima M, Miyazaki T, Kato H and Kuwano H: MiR-150 is associated with poor prognosis in esophageal squamous cell carcinoma *via* targeting the EMT inducer ZEB1. Cancer Sci *104(1)*: 48-54, 2013. PMID: 23013135. DOI: 10.1111/cas.12030

144 Zhang P, Sun Y and Ma L: ZEB1: at the crossroads of epithelial-mesenchymal transition, metastasis and therapy resistance. Cell

Cycle *14(4)*: 481-487, 2015. PMID: 25607528. DOI: 10.1080/15384101.2015.1006048

145 Caramel J, Ligier M and Puisieux A: Pleiotropic roles for ZEB1 in cancer. Cancer Res *78(1)*: 30-35, 2018. PMID: 29254997. DOI: 10.1158/0008-5472.CAN-17-2476

146 Yang X, Wang Q, Dai W, Zhang J and Chen X: Overexpression of zinc finger E-box binding homeobox factor 1 promotes tumor invasiveness and confers unfavorable prognosis in esophageal squamous cell carcinoma. Tumour Biol *35(12)*: 11977-11984, 2014. PMID: 25142232. DOI: 10.1007/s13277-014-2494-8

147 Sun Y, Yu X and Bai Q: miR-204 inhibits invasion and epithelial-mesenchymal transition by targeting FOXM1 in esophageal cancer. Int J Clin Exp Pathol *8(10)*: 12775-12783, 2015. PMID: 26722467.

148 Calissi G, Lam EW and Link W: Therapeutic strategies targeting FOXO transcription factors. Nat Rev Drug Discov *20(1)*: 21-38, 2021. PMID: 33173189. DOI: 10.1038/s41573-020-0088-2

149 Gartel AL: FOXM1 in cancer: Interactions and vulnerabilities. Cancer Res *77(12)*: 3135-3139, 2017. PMID: 28584182. DOI: 10.1158/0008-5472.CAN-16-3566

150 Liao GB, Li XZ, Zeng S, Liu C, Yang SM, Yang L, Hu CJ and Bai JY: Regulation of the master regulator FOXM1 in cancer. Cell Commun Signal *16(1)*: 57, 2018. PMID: 30208972. DOI: 10.1186/s12964-018-0266-6

151 Song L, Wang X and Feng Z: Overexpression of FOXM1 as a target for malignant progression of esophageal squamous cell carcinoma. Oncol Lett *15(4)*: 5910-5914, 2018. PMID: 29552222. DOI: 10.3892/ol.2018.8035

152 Yamamoto S, Inoue J, Kawano T, Kozaki K, Omura K and Inazawa J: The impact of miRNA-based molecular diagnostics and treatment of NRF2-stabilized tumors. Mol Cancer Res *12(1)*: 58-68, 2014. PMID: 24307696. DOI: 10.1158/1541-7786.MCR-13-0246-T

153 Jaramillo MC and Zhang DD: The emerging role of the Nrf2-Keap1 signaling pathway in cancer. Genes Dev *27(20)*: 2179-2191, 2013. PMID: 24142871. DOI: 10.1101/gad.225680.113

154 Rojo de la Vega M, Chapman E and Zhang DD: NRF2 and the hallmarks of cancer. Cancer Cell *34(1)*: 21-43, 2018. PMID: 29731393. DOI: 10.1016/j.ccell.2018.03.022

155 Menegon S, Columbano A and Giordano S: The dual roles of NRF2 in cancer. Trends Mol Med *22(7)*: 578-593, 2016. PMID: 27263465. DOI: 10.1016/j.molmed.2016.05.002

156 Kitamura H and Motohashi H: NRF2 addiction in cancer cells. Cancer Sci *109(4)*: 900-911, 2018. PMID: 29450944. DOI: 10.1111/cas.13537

157 Kitano Y, Baba Y, Nakagawa S, Miyake K, Iwatsuki M, Ishimoto T, Yamashita YI, Yoshida N, Watanabe M, Nakao M and Baba H: Nrf2 promotes oesophageal cancer cell proliferation *via* metabolic reprogramming and detoxification of reactive oxygen species. J Pathol *244(3)*: 346-357, 2018. PMID: 29243822. DOI: 10.1002/path.5021

158 Xia D, Zhang XR, Ma YL, Zhao ZJ, Zhao R and Wang YY: Nrf2 promotes esophageal squamous cell carcinoma (ESCC) resistance to radiotherapy through the CaMKIIα-associated activation of autophagy. Cell Biosci *10*: 90, 2020. PMID: 32760495. DOI: 10.1186/s13578-020-00456-6

159 Shibata T, Kokubu A, Saito S, Narisawa-Saito M, Sasaki H, Aoyagi K, Yoshimatsu Y, Tachimori Y, Kushima R, Kiyono T and Yamamoto M: NRF2 mutation confers malignant potential and resistance to chemoradiation therapy in advanced esophageal squamous cancer. Neoplasia *13(9)*: 864-873, 2011. PMID: 21969819. DOI: 10.1593/neo.11750

160 Jin L, Yi J, Gao Y, Han S, He Z, Chen L and Song H: MiR-630 inhibits invasion and metastasis in esophageal squamous cell carcinoma. Acta Biochim Biophys Sin (Shanghai) *48(9)*: 810-819, 2016. PMID: 27563011. DOI: 10.1093/abbs/gmw073

161 Hasan MR, Sharma R, Saraya A, Chattopadhyay TK, DattaGupta S, Walfish PG, Chauhan SS and Ralhan R: Slug is a predictor of poor prognosis in esophageal squamous cell carcinoma patients. PLoS One *8(12)*: e82846, 2013. PMID: 24367561. DOI: 10.1371/journal.pone.0082846

162 Alves CC, Carneiro F, Hoefler H and Becker KF: Role of the epithelial-mesenchymal transition regulator Slug in primary human cancers. Front Biosci (Landmark Ed) *14*: 3035-3050, 2009. PMID: 19273255. DOI: 10.2741/3433

163 Zhou W, Gross KM and Kuperwasser C: Molecular regulation of Snai2 in development and disease. J Cell Sci *132(23)*: jcs235127, 2019. PMID: 31792043. DOI: 10.1242/jcs.235127

164 Tang P, Yu Z, Zhang K, Wang Y, Ma Z, Zhang S, Chen D and Zhou Y: Slug down-regulation by RNA interference inhibits invasion growth in human esophageal squamous cell carcinoma. BMC Gastroenterol *11*: 60, 2011. PMID: 21599940. DOI: 10.1186/1471-230X-11-60

165 Zhang JX, Chen ZH, Xu Y, Chen JW, Weng HW, Yun M, Zheng ZS, Chen C, Wu BL, Li EM, Fu JH, Ye S and Xie D: Downregulation of MicroRNA-644a promotes esophageal squamous cell carcinoma aggressiveness and stem cell-like phenotype *via* dysregulation of PITX2. Clin Cancer Res *23(1)*: 298-310, 2017. PMID: 27407092. DOI: 10.1158/1078-0432.CCR-16-0414

166 Logan M, Pagán-Westphal SM, Smith DM, Paganessi L and Tabin CJ: The transcription factor Pitx2 mediates situs-specific morphogenesis in response to left-right asymmetric signals. Cell *94(3)*: 307-317, 1998. PMID: 9708733. DOI: 10.1016/s0092-8674(00)81474-9

167 Buckingham M and Rigby PW: Gene regulatory networks and transcriptional mechanisms that control myogenesis. Dev Cell *28(3)*: 225-238, 2014. PMID: 24525185. DOI: 10.1016/j.devcel.2013.12.020

168 Zhang JX, Tong ZT, Yang L, Wang F, Chai HP, Zhang F, Xie MR, Zhang AL, Wu LM, Hong H, Yin L, Wang H, Wang HY and Zhao Y: PITX2: a promising predictive biomarker of patients' prognosis and chemoradioresistance in esophageal squamous cell carcinoma. Int J Cancer *132(11)*: 2567-2577, 2013. PMID: 23132660. DOI: 10.1002/ijc.27930

169 Mu Y, Wang Q, Tan L, Lin L and Zhang B: microRNA-144 inhibits cell proliferation and invasion by directly targeting TIGAR in esophageal carcinoma. Oncol Lett *19(4)*: 3079-3088, 2020. PMID: 32256808. DOI: 10.3892/ol.2020.11420

170 Bensaad K, Tsuruta A, Selak MA, Vidal MN, Nakano K, Bartrons R, Gottlieb E and Vousden KH: TIGAR, a p53-inducible regulator of glycolysis and apoptosis. Cell *126(1)*: 107-120, 2006. PMID: 16839880. DOI: 10.1016/j.cell.2006.05.036

171 Geng J, Yuan X, Wei M, Wu J and Qin ZH: The diverse role of TIGAR in cellular homeostasis and cancer. Free Radic Res *52(11-12)*: 1240-1249, 2018. PMID: 30284488. DOI: 10.1080/10715762.2018.1489133

172 Chu J, Niu X, Chang J, Shao M, Peng L, Xi Y, Lin A, Wang C, Cui Q, Luo Y, Fan W, Chen Y, Sun Y, Guo W, Tan W, Lin D and Wu C: Metabolic remodeling by TIGAR overexpression is a

therapeutic target in esophageal squamous-cell carcinoma. Theranostics *10(8)*: 3488-3502, 2020. PMID: 32206103. DOI: 10.7150/thno.41427

173 Li G, Qi HW, Dong HG, Bai P, Sun M and Liu HY: Targeting deubiquitinating enzyme USP26 by microRNA-203 regulates Snail1's pro-metastatic functions in esophageal cancer. Cancer Cell Int *20*: 355, 2020. PMID: 32760222. DOI: 10.1186/s12935-020-01441-2

174 Stouffs K, Lissens W, Tournaye H, Van Steirteghem A and Liebaers I: Possible role of USP26 in patients with severely impaired spermatogenesis. Eur J Hum Genet *13(3)*: 336-340, 2005. PMID: 15562280. DOI: 10.1038/sj.ejhg.5201335

175 Young MJ, Hsu KC, Lin TE, Chang WC and Hung JJ: The role of ubiquitin-specific peptidases in cancer progression. J Biomed Sci *26(1):* 42, 2019. PMID: 31133011. DOI: 10.1186/s12929-019-0522-0

176 Pal A, Young MA and Donato NJ: Emerging potential of therapeutic targeting of ubiquitin-specific proteases in the treatment of cancer. Cancer Res *74(18)*: 4955-4966, 2020. DOI: 10.1158/0008-5472.CAN-14-1211

177 Liu J, Shaik S, Dai X, Wu Q, Zhou X, Wang Z and Wei W: Targeting the ubiquitin pathway for cancer treatment. Biochim Biophys Acta *1855(1)*: 50-60, 2015. PMID: 25481052. DOI: 10.1016/j.bbcan.2014.11.005

178 Li L, Zhou H, Zhu R and Liu Z: USP26 promotes esophageal squamous cell carcinoma metastasis through stabilizing Snail. Cancer Lett *448*: 52-60, 2019. PMID: 30763716. DOI: 10.1016/j.canlet.2019.02.007

179 Yan S, Jiang H, Fang S, Yin F, Wang Z, Jia Y, Sun X, Wu S, Jiang T and Mao A: MicroRNA-340 inhibits esophageal cancer cell growth and invasion by targeting phosphoserine aminotransferase 1. Cell Physiol Biochem *37(1)*: 375-386, 2015. PMID: 26316084. DOI: 10.1159/000430361

180 Sun C, Zhang X, Chen Y, Jia Q, Yang J and Shu Y: MicroRNA-365 suppresses cell growth and invasion in esophageal squamous cell carcinoma by modulating phosphoserine aminotransferase 1. Cancer Manag Res *10*: 4581-4590, 2018. PMID: 30410394. DOI: 10.2147/CMAR.S157858

181 Ravez S, Spillier Q, Marteau R, Feron O and Frédérick R: Challenges and opportunities in the development of serine synthetic pathway inhibitors for cancer therapy. J Med Chem *60(4)*: 1227-1237, 2017. PMID: 27959531. DOI: 10.1021/acs.jmedchem.6b01167

182 Liu B, Jia Y, Cao Y, Wu S, Jiang H, Sun X, Ma J, Yin X, Mao A and Shang M: Overexpression of phosphoserine aminotransferase 1 (PSAT1) predicts poor prognosis and associates with tumor progression in human esophageal squamous cell carcinoma. Cell Physiol Biochem *39(1)*: 395-406, 2016. PMID: 27372650. DOI: 10.1159/000445633

183 Isozaki Y, Hoshino I, Akutsu Y, Hanari N, Mori M, Nishimori T, Murakami K, Akanuma N, Takeshita N, Maruyama T, Toyozumi T, Takahashi M, Suito H and Matsubara H: Usefulness of microRNA 375 as a prognostic and therapeutic tool in esophageal squamous cell carcinoma. Int J Oncol *46(3)*: 1059-1066, 2015. PMID: 25501018. DOI: 10.3892/ijo.2014.2789

184 Isozaki Y, Hoshino I, Nohata N, Kinoshita T, Akutsu Y, Hanari N, Mori M, Yoneyama Y, Akanuma N, Takeshita N, Maruyama T, Seki N, Nishino N, Yoshida M and Matsubara H: Identification of novel molecular targets regulated by tumor suppressive miR-375 induced by histone acetylation in esophageal squamous cell carcinoma. Int J Oncol *41(3)*: 985-994, 2012. PMID: 22752059. DOI: 10.3892/ijo.2012.1537

185 Zha X, Wang F, Wang Y, He S, Jing Y, Wu X and Zhang H: Lactate dehydrogenase B is critical for hyperactive mTOR-mediated tumorigenesis. Cancer Res *71(1)*: 13-18, 2011. PMID: 21199794. DOI: 10.1158/0008-5472.CAN-10-1668

186 Urbańska K and Orzechowski A: Unappreciated role of LDHA and LDHB to control apoptosis and autophagy in tumor cells. Int J Mol Sci *20(9)*: 2085, 2019. PMID: 31035592. DOI: 10.3390/ijms20092085

187 Wang Z, Tang ZY, Yin Z, Wei YB, Liu LF, Yan B, Zhou KQ, Nian YQ, Gao YL and Yang JR: Metadherin regulates epithelial-mesenchymal transition in carcinoma. Onco Targets Ther 9: 2429-2436, 2016. PMID: 27143938. DOI: 10.2147/OTT.S104556

188 Hu G, Wei Y and Kang Y: The multifaceted role of MTDH/AEG-1 in cancer progression. Clin Cancer Res *15(18)*: 5615-5620, 2009. PMID: 19723648. DOI: 10.1158/1078-0432.CCR-09-0049

189 Yang C, Zheng S, Liu Q, Liu T, Lu M, Dai F, Gao X, Sheyhidin I and Lu X: Metadherin is required for the proliferation, migration, and invasion of esophageal squamous cell carcinoma and its meta-analysis. Transl Res *166(6)*: 614-626.e2, 2015. PMID: 26051629. DOI: 10.1016/j.trsl.2015.05.004

190 Han DL, Wang LL, Zhang GF, Yang WF, Chai J, Lin HM, Fu Z and Yu JM: MiRNA-485-5p, inhibits esophageal cancer cells proliferation and invasion by down-regulating O-linked N-acetylglucosamine transferase. Eur Rev Med Pharmacol Sci *23(7)*: 2809-2816, 2019. PMID: 31002132. DOI: 10.26355/eurrev_201904_17556

191 Maynard JC, Burlingame AL and Medzihradszky KF: Cysteine S-linked N-acetylglucosamine (S-GlcNAcylation), a new post-translational modification in mammals. Mol Cell Proteomics *15(11)*: 3405-3411, 2016. PMID: 27558639. DOI: 10.1074/mcp.M116.061549

192 Gorelik A, Bartual SG, Borodkin VS, Varghese J, Ferenbach AT and van Aalten DMF: Genetic recoding to dissect the roles of site-specific protein O-GlcNAcylation. Nat Struct Mol Biol *26(11)*: 1071-1077, 2019. PMID: 31695185. DOI: 10.1038/s41594-019-0325-8

193 Singh JP, Zhang K, Wu J and Yang X: O-GlcNAc signaling in cancer metabolism and epigenetics. Cancer Lett *356(2 Pt A)*: 244-250, 2015. PMID: 24769077. DOI: 10.1016/j.canlet.2014.04.014

194 Wang Y, Feng J, Zang W, Du Y, Chen X, Sun Q, Dong Z and Zhao G: MiR-499 enhances the cisplatin sensitivity of esophageal carcinoma cell lines by targeting DNA polymerase β. Cell Physiol Biochem *36(4)*: 1587-1596, 2015. PMID: 26159783. DOI: 10.1159/000430321

195 Bergoglio V, Pillaire MJ, Lacroix-Triki M, Raynaud-Messina B, Canitrot Y, Bieth A, Garès M, Wright M, Delsol G, Loeb LA, Cazaux C and Hoffmann JS: Deregulated DNA polymerase beta induces chromosome instability and tumorigenesis. Cancer Res *62(12)*: 3511-3514, 2002. PMID: 12067997.

196 Goodman MF: Error-prone repair DNA polymerases in prokaryotes and eukaryotes. Annu Rev Biochem *71*: 17-50, 2002. PMID: 12045089. DOI: 10.1146/annurev.biochem.71.083101.124707

197 Goellner EM, Svilar D, Almeida KH and Sobol RW: Targeting DNA polymerase ß for therapeutic intervention. Curr Mol Pharmacol *5(1)*: 68-87, 2012. PMID: 22122465.

198 Cui XB, Peng H, Li RR, Mu JQ, Yang L, Li N, Liu CX, Hu JM, Li SG, Wei Y, Laibo-Yin, Zhou H, Li F and Chen YZ:

MicroRNA-34a functions as a tumor suppressor by directly targeting oncogenic PLCE1 in Kazakh esophageal squamous cell carcinoma. Oncotarget *8(54)*: 92454-92469, 2017. PMID: 29190930. DOI: 10.18632/oncotarget.21384

199 Qin Y, Zhang Y, Tang Q, Jin L and Chen Y: SQLE induces epithelial-to-mesenchymal transition by regulating of miR-133b in esophageal squamous cell carcinoma. Acta Biochim Biophys Sin (Shanghai) *49(2)*: 138-148, 2017. PMID: 28069586. DOI: 10.1093/abbs/gmw127

200 Rupaimoole R and Slack FJ: MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. Nat Rev Drug Discov *16(3)*: 203-222, 2017. PMID: 28209991. DOI: 10.1038/nrd.2016.246

201 Mollaei H, Safaralizadeh R and Rostami Z: MicroRNA replacement therapy in cancer. J Cell Physiol *234(8)*: 12369-12384, 2019. PMID: 30605237. DOI: 10.1002/jcp.28058

202 Forterre A, Komuro H, Aminova S and Harada M: A comprehensive review of cancer MicroRNA therapeutic delivery strategies. Cancers (Basel) *12(7)*: 1852, 2020. PMID: 32660045. DOI: 10.3390/cancers12071852

203 Karkhane M, Lashgarian HE, Hormozi M, Fallahi S, Cheraghipour K and Marzban A: Oncogenesis and tumor inhibition by MicroRNAs and its potential therapeutic applications: a systematic review. Microrna *9(3)*: 198-215, 2020. PMID: 31686643. DOI: 10.2174/2211536608666191104103834

204 Zhao L, Zhou S and Gustafsson JÅ: Nuclear receptors: Recent drug discovery for cancer therapies. Endocr Rev *40(5)*: 1207-1249, 2019. PMID: 30869771. DOI: 10.1210/er.2018-00222

205 Bushweller JH: Targeting transcription factors in cancer - from undruggable to reality. Nat Rev Cancer *19(11)*: 611-624, 2019. PMID: 31511663. DOI: 10.1038/s41568-019-0196-7

206 Lambert M, Jambon S, Depauw S and David-Cordonnier MH: Targeting transcription factors for cancer treatment. Molecules *23(6)*: 1479, 2018. PMID: 29921764. DOI: 10.3390/molecules 23061479

207 Bhagwat AS and Vakoc CR: Targeting transcription factors in cancer. Trends Cancer *1(1)*: 53-65, 2015. PMID: 26645049. DOI: 10.1016/j.trecan.2015.07.001

208 Shiroma Y, Takahashi RU, Yamamoto Y and Tahara H: Targeting DNA binding proteins for cancer therapy. Cancer Sci *111(4)*: 1058-1064, 2020. PMID: 32073717. DOI: 10.1111/cas.14355

209 Weyandt JD, Thompson CB, Giaccia AJ and Rathmell WK: Metabolic alterations in cancer and their potential as therapeutic targets. Am Soc Clin Oncol Educ Book *37*: 825-832, 2017. PMID: 28561705. DOI: 10.1200/EDBK_175561

210 DeBerardinis RJ and Chandel NS: Fundamentals of cancer metabolism. Sci Adv *2(5)*: e1600200, 2016. PMID: 27386546. DOI: 10.1126/sciadv.1600200

211 Vander Heiden MG and DeBerardinis RJ: Understanding the Intersections between Metabolism and Cancer Biology. Cell *168(4)*: 657-669, 2017. PMID: 28187287. DOI: 10.1016/j.cell.2016.12.039

212 Hashemi A and Gorji-Bahri G: MicroRNA: Promising roles in cancer therapy. Curr Pharm Biotechnol *21(12)*: 1186-1203, 2020. PMID: 32310047. DOI: 10.2174/1389201021666200420101613

213 Zhang Y, Wang Z and Gemeinhart RA: Progress in microRNA delivery. J Control Release *172(3)*: 962-974, 2013. PMID: 24075926. DOI: 10.1016/j.jconrel.2013.09.015

214 Jones D: Setbacks shadow microRNA therapies in the clinic. Nat Biotechnol *36(10)*: 909-910, 2018. PMID: 30307922. DOI: 10.1038/nbt1018-909

215 Anastasiadou E, Seto AG, Beatty X, Hermreck M, Gilles ME, Stroopinsky D, Pinter-Brown LC, Pestano L, Marchese C, Avigan D, Trivedi P, Escolar DM, Jackson AL and Slack FJ: Cobomarsen, an Oligonucleotide Inhibitor of miR-155, Slows DLBCL Tumor Cell Growth *In Vitro* and *In Vivo*. Clin Cancer Res *27(4)*: 1139-1149, 2021. PMID: 33208342. DOI: 10.1158/1078-0432.CCR-20-3139

216 Witten L and Slack FJ: miR-155 as a novel clinical target for hematological malignancies. Carcinogenesis *41(1)*: 2-7, 2020. PMID: 31711135. DOI: 10.1093/carcin/bgz183

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