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Review

MicroRNAs Involved in Small-cell Lung Cancer as Possible Agents for Treatment and Identification of New Targets

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Abstract. *Small-cell lung cancer, a neuro-endocrine type of lung cancers, responds very well to chemotherapy-based agents. However, a high frequency of relapse due to adaptive resistance is observed. Immunotherapy-based treatments with checkpoint inhibitors has resulted in improvement of treatment but the responses are not as impressive as in other types of tumor. Therefore, identification of new targets and treatment modalities is an important issue. After searching the literature, we identified eight down-regulated microRNAs involved in radiation- and chemotherapy-induced resistance, as well as three up-regulated and four down-regulated miRNAs with impacts on proliferation, invasion and apoptosis of small-cell lung cancer cells in vitro. Furthermore, one up-regulated and four down-regulated microRNAs with in vivo activity in SCLC cell xenografts were identified. The identified microRNAs are candidates for inhibition or reconstitution therapy. The corresponding targets are candidates for inhibition or functional reconstitution with antibody-based moieties or small molecules.*

Small-cell lung cancer (SCLC) is an exceptionally lethal malignancy comprising 13-15% of all lung cancer (1), with 250,000 cases diagnosed annually worldwide (1). SCLC is highly sensitive to platinum-based chemotherapy, topoisomerase inhibitor etoposide, and to lurbinectidin, a recently approved DNA binder (2, 3). However, disease recurrence and metastasis to the brain, adrenal glands, bone and liver after treatment remains an issue (2). Inactivating mutations in retinoblastoma (*RB*) or *TP53* are most commonly observed, however, these alterations are not druggable and, in contrast to non-small-cell lung cancer no tractable drivers or fusion proteins have been observed (4). Monoclonal antibodies nivolumab and pembrolizumab, directed against checkpoint inhibitors, have been approved as first-line treatment of SCLC together with chemotherapy and for treatment of relapsed disease (5). However, the therapeutic benefit is not as pronounced as observed with other types of tumor (5). Furthermore, SCLC subtypes have been identified based on differential expression of transcription factors achaete-scute homolog (ASCL1), neurogenic differentiation factor (NeuroD1), yes-associated protein (YAP1) and POU class 2 homeobox 3 (POU2F3) (6). These subtypes might respond to drugs with different vulnerability (6). Several agents targeting T-cell immunoreceptor with Ig and ITIM domains (TIGIT), cytotoxic T-lymphocyte antigen 4 (CTLA4), or cyclin-dependent kinases 4 and 6 are in phase III clinical studies or under Food and Drug Administration review (7). Nevertheless, there is an urgent need to identify new targets and treatment modalities for SCLC. Here, we focus on microRNAs (miRs) as therapeutic agents and as tools for identification of SCLC-related targets for therapeutic intervention.

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MicroRNAs – Role in Oncology

miRs are synthesized by RNA polymersase II in the nucleus as precursor RNAs, processed and exported into the cytoplasm (8-10). One strand of a 22 nucleotides (nts) complex is maintained (guide strand), the other strand (passenger strand) is discarded (8-10). The guide strand binds to the 3'-untranslated region of corresponding mRNAs and induces their degradation or inhibits their translation (8-10). A single miR can interact with several different mRNAs and therefore can interfere with several pathways and has the potential to rewire oncogenic pathways (11). miRs can exert an oncogenic or tumor-suppressive role, depending on the context (12). A

tumor-suppressive role is mediated by *miR-16-1* and *miR-15a* by targeting anti-apoptotic protein BCL2 apoptosis regulator (BCL2). Their deletion in mice causes B-cell chronic lymphocytic leukemia corresponding to the disease in humans and its cytogenetic characteristics (13, 14). The oncogenic role of miRs was demonstrated by induction of hepatocellular carcinoma through liver-specific expression of *miR-221* in transgenic mice (15). miRs can have an impact on all stages of carcinogenesis, including metastasis and anti-tumoral immune response (16). We recently summarized the impact of miRs on growth and metastasis of hepatocellular carcinoma (17), pancreatic cancer (18), non-small-cell lung carcinoma (19), breast cancer (20) and prostate cancer (21). In this review, we focus on the role of miRs with respect to chemoresistance, tumor growth and metastasis of SCLC.

miRs Involved in Chemoresistance and Radioresistance of SCLC

All of the miRs discussed are down-regulated in SCLC-cancer related cell lines or clinical specimen in comparison to corresponding controls.

miR-7. *miR-7* (Figure 1) affects the multidrug-resistance protein *A*TP-binding cassette subfamily C member 1 (ABCC1) (22), inward-rectifier potassium ion channel 2.1 (KIR2.1) (23) and poly (ADP-ribose) polymerase 1 (PARP1) (24).

ABCC1 expression is inversely correlated with *miR-7* (22). ABCC1 is a transmembrane drug transporter containing three membrane-spanning domains and two cytosolic nucleotide-binding domains (25) and is expressed in many types of multidrug-resistant cancer (26). Overexpression of ABCC1 is predictive for resistance to chemotherapy in SCLC (27, 28). A low-level expression of *miR-7* correlated with shorter overall survival in patients with SCLC (22). In the SCLC cell line H69AR, *miR-7* down-regulation was shown to be responsible for resistance to adriamycin and etoposide (22, 29).

miR-7 also targets KIR2.1, a member of the classical inward rectifying potassium channel family (23, 30-32). *KIR2.1* was up-regulated five-fold in H69AR cells in comparison to H69 SCLC cells (23). KIR2.1 induced resistance to apoptosis following exposure to chemotherapeutic drugs (23). Overexpression of KIR2.1 in H69 and H466 SCLC cells enhanced their growth in immuno-deficient mice (23). Up-regulation of *miR-7* sensitized H69AR cells to adriamycin, cisplatin and etoposide (23). RAS-protein kinase C–mitogen-activated protein kinase (MEK) signaling was identified as an important inducer of KIR2.1, which was down-regulated by RAS-protein kinase C inhibitor staurosporine and MEK inhibitor UO126 (23).

PARP1 was identified as a target in doxorubicin-resistent SCLC cell line H69AR in comparison to H69 parental cells (24). PARP1 was resolved as a target of *miR-7* (24, 34). Inhibition of *miR-7* resulted in increased homologous repair in doxorubicin-resistant SCLC cells (24). *miR-7* reduced expression of breast cancer susceptibility protein 1 (BRCA1) and repair protein RAD51 homolog1 (RAD51), and discrupted homologous recombination-based repair, leading to doxorubicin resistance by targeting PARP1 (24). PARP1 has a multi-faceted role in DNA repair and chromatin remodeling (35). PARP1 inhibitors are approved anticancer agents based on a synthetic-lethality based mode of action (36-38).

miR-22. *miR-22* (Figure 1) was down-regulated in NCI-466 SCLC cells and inhibited radiosensitivity by targeting Werner helicase-interacting protein-1 (WRNIP1) (39). WRNIP1 is an ATPase which can protect replication forks and co-operates with RAD51 to safeguard the integrity and maintenance of the genome (40-42). Overexpression of *miR-22* promoted apoptosis and inhibited migration of NCI-466 cells (39).

miR-24-3p. Autophagy is a strategy by which resistance to chemotherapy is conferred (43, 44). Etoposide- and cisplatin -resistant SCLC cells exhibited increased autophagy (45). *miR-24*-3p (Figure 1) was down-regulated in SCLC cells and expression of autophagy-related 4A cysteine peptidase (ATG4A) was blocked (45). Expression of *miR-24*-3p can suppress autophagy of SCLC cells by directly targeting ATG4A (45). It has been shown that inhibitors of autophagy can sensitize chemoresistant cells to anticancer therapy in clinical trials (45, 46).

miR-100. *miR-100* (Figure 1) was shown to target homeobox transcription factor HOXA1, which was associated with poor prognosis in patients with SCLC, and its down-regulation mediated chemoresistance (47). HOXA1 was found to be expressed in 46% (29/63) of tumors from patients with SCLC. Expression of *miR-100* in multidrug-resistant SCLC cell line H69AR reversed resistance to cisplatin and etoposide (47). HOXA1 is involved in progression and prognosis of several types of tumor. It mediates tumor proliferation and poor prognosis in gastric cancer *via* cyclin D1 (48); enhances proliferation, invasion and metastasis of prostate cancer cells (49); and correlates with poor prognosis in patients with hepatocellular carcinoma (50).

miR-138. *miR-138* (Figure 1) was down-regulated in SCLC tissues and three corresponding cell lines (51). In NCI-H2081 SCLC cells, *miR-138* reduced cell growth and inhibited cell-cycle progression (51). Histone H2A variant X (H2AX) was identified as a target of *miR-138* (51). *H2AX* knockdown achieved a similar effect as observed for *miR-138* overexpression, whilst its induction abolished *miR-138*-mediated SCLC cell growth and inhibition of cell-cycle progression (51). Expression of *miR-138* was shown to confer SCLC cells with greater DNA-repair capacity and reduced

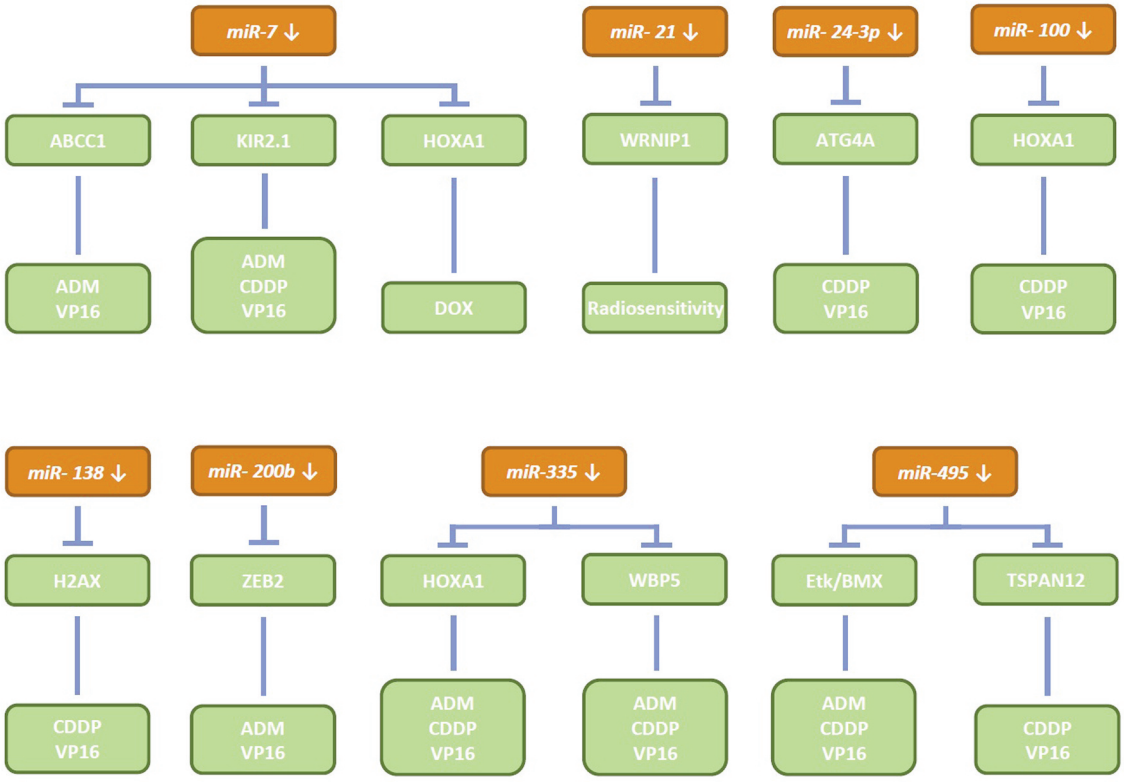

Figure 1. *miRs involved in chemo- and radio-resistance of small-cell lung cancer (SCLC) cells. Downward arrows indicate down-regulation of miRs in SCLC in comparison to controls. ABCC1: ATB binding cassette subfamily C member; ADM: Adriamycin; ATG4A: autophagy-related protein 4; BMX: cytoplasmic tyrosine kinase BMX; CDDP: cisplatin; ETK: non-receptor tyrosine kinase Etk; H2AX: histone H2AX; HOXA1: homebox protein HOXA1; KIR2.1: inward rectifier ion channel 2.1; PARP1: poly (ADP ribose)-polymerase 1; TSPAN 12: tetraspanin 12; VP16: etoposide; WBP5: ww domain-binding protein 1; WRNIP1: ATPase WRNIP1; ZEB2: zinc finger E-box-binding homeobox 2.*

their resistance to chemotherapeutic agents (51). H2AX is involved in double-stranded DNA repair, chromatin remodeling and contributes to nucleosome formation (52-55).

miR-200b. *miR-200b* (Figure 1) targets zinc finger E-box homeobox2 (ZEB2), which correlated with poor pathologic stage and shorter survival (35). ZEB2 was found to be expressed in 23.5% (16/68) of cases of SCLC (56). Inhibition of ZEB2 expression making use of small-interfering RNA (siRNA), sensitized SCLC-related cells to chemotherapeutic drugs by enhancing drug-induced apoptosis accompanied by S-phase arrest (56). ZEB2 is a transcription factor with eight zinc fingers and a homeodomain (57). ZEB2 has been identified as a regulator of nervous system development (58, 59). In cancer, ZEB2 plays an instrumental role in epithelial mesenchymal transition (EMT), cancer-stem cell traits, apoptosis, survival, tumor recurrence and metastasis (60).

miR-335. *miR-335* (Figure 1) was found to target WW domain-binding protein 5 (WBP5), expression of which was 10-fold increased in H69AR compared to H69 SCLC cells. WBP5 induced multidrug resistance by promoting cell proliferation and inhibiting apoptosis in H69AR cells (61). Expression of WBP5 was associated with shorter survival in patients with SCLC (61). WW binding domains are typically 35-40 amino acids in length and can interact with a variety of different peptide ligands, including motifs with core proline-rich sequences (62). WBP5 was shown to be involved in multidrug resistance of SCLC through the Hippo pathway [WBP5-tyrosine kinase ABL-mammalian Ste-20-like kinase (MST2)-yes-associated protein1 (YAP1)] pathway (61). WBP5 can induce nuclear accumulation of YAP1, a transcription factor which induces genes involved in development and survival (63). Inhibition of YAP1 by verteporfin was shown to blunt multidrug resistance in H69AR cells (61). WBP5 can bind to ABL, an upstream activator of ser-thr kinase MST2 of the Hippo pathway (64,65). It was shown that WBP5 promotes tumor growth and resistance of H69 cells to adriamycin and cisplatin in nude mice (61).

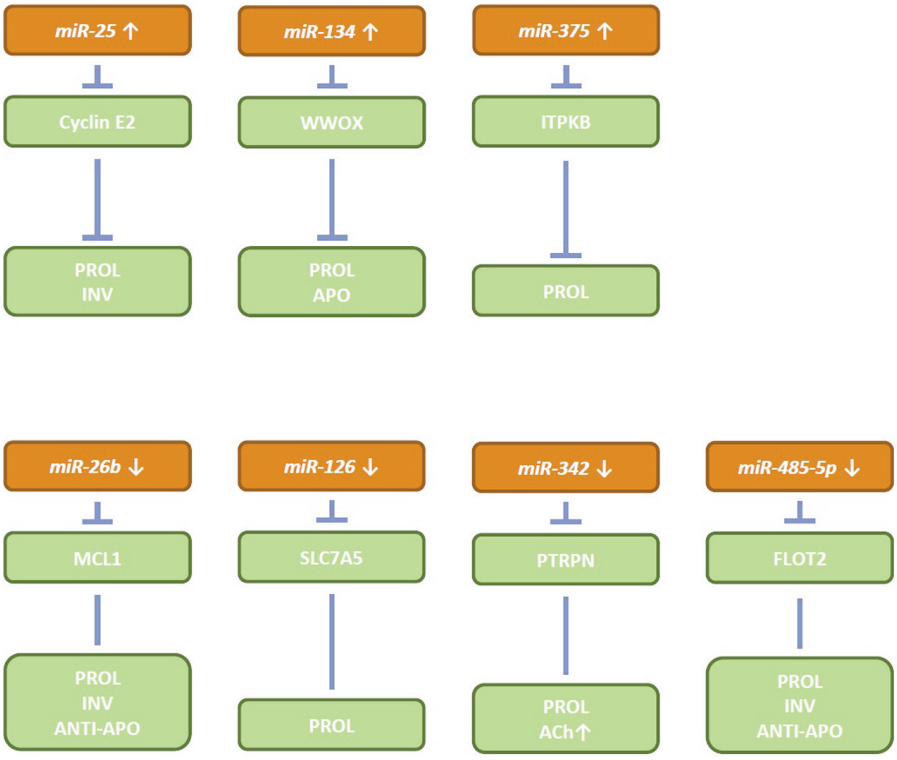

Figure 2. *miRs Up- and down-regulated in small-cell lung cancer with in vitro activity. Upward arrows indicate increased expression and downward arrows point to decreased expression of the corresponding miRs in comparison to control tissues. ACh: Acetyl-choline; APO: apoptosis; FLOT2: flotillin 2; PTPRN: protein tyrosine phosphatase receptor type N; INV: invasion; ITPKB: inositol-triphosphate-3 kinase B; MCL1: myeloid cell differentiation protein 1; PROL: proliferation; SLC7A5: solute carrier family 7A5; WWOX: WW containing oxidoreductase.*

miR-335 was also down-regulated in SCLC cell lines H69AR and H446DDP (66). Overexpression of *miR-335* inhibited migration of H69AR and H446DDP cells *in vitro* and their tumor growth *in vivo*, whereas its inhibition resulted in opposite effects (66). PARP1 was identified as a direct target of *miR-335* (66). Chemoradiosensitiviy of SCLC cells was increased by down-regulation of *PARP1* and nuclear factor κB (66). Down-regulation of *miR-335* resulted in resistance to adriamycin, cisplatin and etoposide in SCLC cell lines H69AR and H446DDP (66). PARP1 detects single-strand DNA breaks and recruits other enzymes involved in DNA repair (67, 68).

miR-495. *miR-495* (Figure 1) was down-regulated in SCLC and inhibited chemoresistance by targeting endothelial tyrosine kinase/bone marrow X kinase (ETK/BMX) (69) and tetraspanin 12 (TSPN12) (70). Functional assays were performed in SCLC cell lines NCI-H446, NCI-H69 and their multidrug-resistant derivatives H446AR and H69AR (69, 70). *miR-495* was expressed at a lower level in SCLC compared to normal lung tissues (69, 70).

miR-495 inhibited apoptosis induced by chemotherapeutic agents such as adriamycin, cisplatin and etoposide by targeting ETK/BMX (69). In nude mice, antagomirs directed against *miR-495* induced rapid growth of xenografts derived from H69 and H446 cells (69). Down-regulation of *miR-495* promoted proliferation, migration invasion and tumor growth of H446 and H69 SCLC *in vitro* and *in vivo* (69). ETK/BMX has been shown to mediate drug resistance in SCLC (71), to regulate the cytoskeleton and migration (72), and to up-regulate vascular endothelial growth factor (73). ETK/BMX has also been identified as a mediator of resistance in acute myeloid leukemia (74) and as a regulator of multiple tyrosine kinases in hormone-refractory prostate cancer (75).

miR-495 was also found to target TSPAN12, which is related to resistance to cisplatin and etoposide (60). TSPAN12 promoted proliferation, migration and tumor growth in drug-resistant SCLC cells H466AR and H69AR (60). TSPAN12 belongs to the tetraspanin family of transmembrane receptors characterized by four transmembrane domains and two extracellular loops (76). Tetraspanins are involved in signaling platforms by forming tetrapanin-enriched microdomains (77). Tetraspanins can mediate tumor-promoting but also metastasis-inhibitory processes (78-80).

miRs Up-regulated in SCLC With Activity in Preclinical *In Vitro* Systems

miR-25. *miR-25* (Figure 2) was up-regulated in SCLC cell lines and tissues (81). Down-regulation of *miR-25* induced cell-cycle arrest and inhibited invasive capability of H510 SCLC cells (81). Overexpression of *miR-25* reversed the effect of *miR-25* down-regulation in H510 cells (81). *miR-25* acted as an oncogene in SCLC cell lines (81). Cyclin E2 has been identified as a direct target of *miR-25*. These findings seem to be counterintuitive since cyclin E has been identified as a regulator of S-phase activity by binding to and activating cyclin-dependent kinase 2 and by phosphorylation of pocket proteins initiating a cascade of events that leads to the expression of S-phase-specific genes (82, 83). A role of cyclin E in DNA replication, control of genomic stability and regulation of the centrosome cycle has also been reported (82, 83). Cyclin E2 is aberrantly expressed in many types of tumors and is increased in cancer-derived cell lines (84). Overexpression of cyclin E in transgenic mice was shown to induce cancer by acting as a dominant oncogene (85). Due to its role in proliferation and apoptosis, cyclin E2 may be an important target for cancer therapy (86). However, it was shown that cyclin E is dispensable for the development of higher eukaryotes and for the division of eukaryotic cells (85). In any case, down-regulation of cyclin E2 in SCLC as reported in (81) might activate a novel tumor-promoting pathway which has to be resolved in further detail.

miR-134. In H69 SCLC cells, *miR-134* (Figure 2) promoted growth, inhibited apoptosis and activated the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway (87). WW domain-containing oxidoreductase (WWOX) has been identified as a direct target of *miR-134* (87). WWOX has two WW domains responsible for protein–protein interactions and a short dehydrogenase/reductase domain which catalyses conversion of low-molecular-weight ligands, most likely steroids (88). Ectopic expression of WWOX inhibited anchorage-dependent growth of MDA-MB-435 and T47D breast cancer cells and attenuates tumorigenicity of MDA-MB-435 cells *in vivo* (89). In lung cancer, *WWOX* gene restoration prevented tumor growth *in vitro* and *in vivo* (89). WWOX localizes to the Golgi apparatus and behaves as a tumor suppressor (90). WWOX is frequently down-regulated in human tumors (91, 92).

miR-375. *miR-375* (Figure 2) was found to be up-regulated in lung adenocarcinoma and SCLC, and down-regulated in lung squamous cell carcinoma (93). *miR-375* promoted proliferation of NCI-H82 SCLC cells (93). Inositol-triphosphate-3 kinase B (ITPKB) was identified as a target of *miR-375* (93). ITPKB regulates inositol phosphate metabolism by phosphorylation of second messenger inositol-1,4,5 triphosphate (94, 95). ITPKB is associated with the Ca signaling pathway and is enriched at actin filaments and invaginations of the nuclear envelope (96). ITPKB also regulates immune functions and is required for B- and T-cell development (96). The role of *miR-375* and down-regulation of *ITPKB* in SCLC remains to be investigated in further detail.

miRs Down-regulated in SCLC With Activity in Preclinical *In Vitro* Systems

miR-26a. Low level expression of *miR-26a* (Figure 2) was detected in SCLC cell lines NCI-H196, NCI-H466 and NCI-H1688 in comparison to MRC5 non-transformed control cells (97). Transfection of these cell lines with a *miR-26a* mimic suppressed proliferation, migration and colony formation (97). Myeloid cell leukemia protein 1 (MCL1) has been identified as a target of *miR-26a* (97). MCL1 is a member of the BCL2 family and plays a role in inhibition of apoptosis induced by tumor necrosis factor-related apoptosis-inducing ligand (98, 99). Inhibition of MCL1 with small molecules has been pursued in several types of cancer, such as myeloma, follicular lymphoma and advanced SCLC in advanced clinical studies (100-102). MCL1 inhibition has been shown to be effective against a subset of SCLCs with high MCL1 and low B-cell lymphoma-extra large (BCL-XL) expression (101).

miR-126. *miR-126* (Figure 2) inhibited proliferation of H69 SCLC cells by causing delay in the G_1 phase of the cell-cycle (102). *miR-126* has been identified as a direct target of solute carrier family 7, member 5 (SLC7A5) (102). Suppression of SLC7A5 by RNAi delayed SCLC cells in the G_1 phase (103). SLC7A5 is part of cluster of differentiation 98 (CD98), and also referred to as large neutral amino acid transporter 1. The other component of CD98 is the CD98 heavy subunit protein encoded by the SCL3A2 gene. CD98 preferentially transports branched chain and aromatic amino acids and is overexpressed in several types of cancer (103-105). SCL7A5 can activate mechanistic target of rapamycin (mTOR), which phosphorylates p70S6 kinase and eukaryotic translation factor 4E-binding protein 1 (4EBP1), resulting in production of growth-promoting proteins (106). mTOR is activated in a large percentage of SCLCs and genetic alterations in the phosphatidylinositol-4,5-bisphosphate 3-kinase/AKT serine/threonine kinase 1/mTOR pathway have been identified in 36% of patients with SCLC (107).

miR-342. Protein tyrosine phosphatase receptor type N (PTPRN), also known as islet antigen 2 (IA-2), was identified as a target of *miR-342* (Figure 2) in SCLC cell lines NCI-H82 and NCI-345 (108). Down-regulation of *PTPRN* by siRNA suppressed SCLC growth as well as cell acetyl choline (ACh)

content and secretion (109). ACh rescued the inhibitory effects of *PTPRN* siRNA and of *miR-342* mimic on SCLC proliferation (109). ACh is an autocrine growth factor which facilitates SCLC growth (109). PTPRN is a transmembrane tyrosine receptor phosphatase and has an important role in secretion of hormones and neurotransmitters in SCLC cell lines, such as follicle-stimulating hormone, insulin, luteinizing hormone, dopamine, renin and norepinephrine (110, 111). PTPRN is highly expressed in tumors and cell lines of neuro-endocrine origin (112). It also has been identified as an auto-antigen that is reactive with sera of patients with insulin-dependent diabetes mellitus (112).

miR-485-5p. *miR-485*-5p (Figure 2) was reduced in SCLC tissues compared to adjacent normal tissues (113). *miR-485*-5p inhibited proliferation, migration and invasion of NCI-H466 and NCI-485-5p SCLC cell lines (113). Flotillin 2 (FlOT2) has been identified as a target of *miR-485*-5p (113). *FLOT2* was found to be up-regulated in SCLC tissues and correlated with worse prognosis (113). FLOT1 and -2 are lipid-raft marker proteins which assemble into heterotetramers, forming molecular scaffolds to regulate clustering at the plasma membrane (114, 115). They are involved in signal transduction, nerve regeneration, endocytosis and lymphocyte activation (114, 115). Up-regulation of FLOT2 is related to lymph node metastasis and poor prognosis in patients with solid tumors (116).

Dysregulated miRs With Activity in Preclinical In Vivo Models of SCLC

Up-regulated miRs

miR-665. Inhibition of *miR-665* (Figure 3) attenuated proliferation, invasion and migration of NCI-H446 SCLC cells (117). *In vivo*, inhibition of *miR-665* led to attenuation of tumor growth (117). Lethal giant larvae protein homolog-1 (LLGL1) was identified as a target of *miR-665* (117). LLGL1 is part of the cytoskeletal network and is associated with non-muscle myosin II heavy chain (117). Overexpression of LLGL1 inhibited proliferation and migration, and increased cellular adhesion and apoptosis (118, 119). Loss of LLGL1 reduced cellular adhesion and dissemination in colorectal cancer, melanoma and gastric cancer; its reduced expression has been noted in lung squamous cell carcinoma (120-123).

Down-regulated miRs

miR-216a-5p. *miR-216a*-5p (Figure 3) reduced proliferation and migration of H69 SCLC cells (124). *miR-216a*-5p targeted BCL2 and modulated BCL2-like protein (BAX) and BCL2 antagonist of cell death (BAD) (124). *In vivo* inhibition of *miR-216a*-5p promoted tumor growth of H69-derived xenografts in mice, whereas a *miR-216* mimic inhibited it (124). BCL2 is an anti-apoptotic protein which is expressed in SCLC (125, 126). BCL2 inhibitor venetoclax was shown to be active in preclinical SCLC-related *in vitro* and *in vivo* systems with high BCL2 expression (127). Venetoclax is approved for chronic lymphocytic leukemia and small lymphocytic leukemia, and is also part of a combination therapy for acute myeloid leukemia (128). Currently clinical studies of treatment of relapsed or refractory SCLC with oral venetoclax in combination with irinotecan and venetoclax in combination with atezolizumab are underway (NCI04543916).

miR-335. Investigations into the role of *miR-335* (Figure 3) were performed with SCLC cells lines SBC-3 and SBC-5. The latter gives rise to bone metastasis in immuno-deficient mouse models, SBC-3 does not. Reduced expression of *miR-335* in SBC-5 in comparison to SBC-3 cells was observed (129). Overexpression of *miR-335* in transfected SBC-5 cells reduced proliferation, migration and colony formation. Skeletal lesions from *miR-335*-transfected SBC-5 cells were not observed in immunodeficient mice (129). Insulin-like growth factor receptor 1 (IGF-1R) and osteoblast receptor activator of nuclear κB ligand (RANKL) were identified as targets for *miR-335* (129). IGF-1R promotes proliferation, invasion, migration and inhibits apoptosis of tumor cells (130). IGF-1R knock-out mice exhibit reduced bone metastasis of breast cancer xenografts (131). Prerequisite for osteolytic metastases is the activation of osteoclasts. Osteoblasts secrete RANKL which interacts with osteoclast precursors displaying RANK receptor on their surface, resulting in their maturation into functional osteoclasts. Osteoblasts also produce osteoprotegerin, a soluble decoy receptor which can block RANK/RANKL signaling (132-134). *miR-335* inhibits IGF-1R and RANKL, two validated mediators of bone metastasis.

miR-450. Down-regulation of *miR-450* (Figure 3) correlated with reduced survival in patients with SCLC (135). *miR-450* inhibited proliferation and invasion of H510A SCLC cells and growth as xenografts implanted into immunodeficient mice (135). Interferon regulatory factor 2 (IRF2) was identified as a target of *miR-450* (135). Overexpression of IRF2 in H510A cells abrogated the inhibitory effects of *miR-450* (136). IRF2 is a member of IRF protein family which possess an *N*-terminal DNA binding domain characterized by five well-conserved tryptophan-rich repeats recognizing IFN-stimulated response elements and a *C*-terminal region which mediates interactions with family members, transcription factors and co-factors conferring specific activities on each IRF (136, 137). IRF2 acts as an oncogene and is involved in regulation of histone 4 gene transcription (138, 139). Overexpression of IRF2 promotea the growth of pancreatic cancer cells (140). In colorectal cancer, IRF2 has been identified as a driver of immune suppression and immune therapy resistance (141).

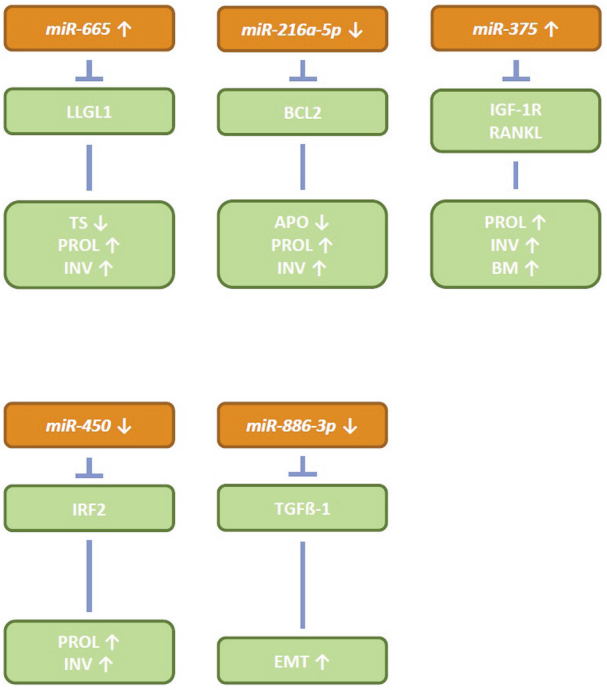

Figure 3. *miRs Up- and down-regulated with activity in preclinical small-cell lung cancer-related in vivo models. Upward arrows: Up-regulated miRs; downward arrows: down-regulated miRs. APO: Apoptosis; BCL2: BCL2 apoptosis regulator; BM: bone metastasis; EMT: epithelial–mesenchymal transition; IGF-1R: insulin-like growth factor receptor 1; INV: invasion; IRF2: interferon regulatory factor 2; LLGL1: lethal giant larvae protein homolog 1; PROL: proliferation; RANK: receptor activator of NFκB ligand; RANKL: RANK ligand; TGFβ1: transforming growth factor β1; TS: tumor suppressor.*

miR-886-3p. *miR-886*-3p (Figure 3) was down-regulated in SCLC (141). In NCI-H446 and NCI-H1688, overexpression of *miR-886*-3p induced mesenchymal–epithelial transition, a change in cellular phenotype from spindle shape to round shape (141). Transforming growth factor β1 (TGFβ1) has been identified as a target of *miR-886*-3p (141). *miR-886-3p*-mediated mesenchymal epithelial transition was induced by suppression of TGFβ (141). Intratumoral injection of a *miR-886*-3p conjugate to cholesterol resulted in necrosis of tumor tissue and suppression of intramuscular invasion (141). Suppression of lung cancer xenograft growth of NCI-H446 cells was observed after systemic delivery of a cholesterol conjugated *miR-886*-3p mimic after tail vein injection of tumor cells. Targeting EMT by either inhibition of TGFβ or by administration of *miR-886*-3p may be a concept for treatment of SCLC which has to be validated in further detail. EMT is a basic principle of tumor progression (142-144).

Conclusion

We identified miRs which affect chemoresistance and radioresistance, as well as *in vitro* and *in vivo* properties of SCLC cell lines. Up-regulated miRs are candidates for inhibition or reconstitution of the corresponding targets. Down-regulated miRs are candidates for reconstitution therapy or inhibition of the corresponding targets with small molecules or antibody-related entities.

Up-regulated miRs can be inhibited with miR antagonists, which are single-stranded RNAs composed of 12-25 nucleotides complementary to the corresponding mRNA or with RNA sponges (145, 146). The latter are composed of multiple miR-binding sites competing with binding of miRs to corresponding mRNA (145, 146). In the case of down-regulated miRs, reconstitution therapy is the indicated therapeutic intervention (147, 148) or re-expression of the corresponding targets, an approach which faces druggability issues due to nonspecific interactions.

Eight down-regulated miRs were found to mediate chemo/radioresistance (Figure 1). They are candidates for reconstitution therapy. PARP1 (*miR-335)* can be inhibited by several approved small molecules and is a validated target (35, 36). ETK (BMX) (*miR-495)*, TSPAN12 (*miR-495)* and KIR2.1 (*miR-7)* are druggable with small molecules or antibody-derived entities. However, the role of the identified miRs in resistance of relapsed SCLC needs to be validated in more detail.

Three up-regulated and four down-regulated miRs affecting proliferation, invasion and apoptosis of SCLC cell lines *in vitro* were identified (Figure 2). MCL1, which is targeted by *miR-26a*, seems to be a promising target. MCL1 inhibition has been shown to be effective in a subset of preclinical SCLC-related *in vitro* models with high MCL1 and low BCL-xL expression (101). PTPRN (*miR-342)* and SCL7A5 (*miR-126)* are druggable targets and the corresponding miRs are candidates for miR-inhibitory agents. However, more target validation experiments are necessary to resolve the relevance of the latter targets.

Furthermore, one up-regulated and four down-regulated miRs with efficacy in preclinical SCLC-related *in vivo* models were identified (Figure 3). The down-regulated miRs are candidates for substitution therapy. BCL2 (*miR-216*-5p) is inhibited by venetoclax and it has been shown that venetoclax is effective in preclinical *in vivo* models with high BCL2 expression (127). *miR-335* targets IGF-1R and RANKL, which mediate proliferation, invasion and bone metastasis of SCLC and both represent druggable targets (130, 132). *miR-886*-3p inhibits TGFβ1, a possible target for interfering with EMT (143, 144). For these miRs and corresponding targets, more target validation experiments in non-small-cell lung carcinoma-related systems are necessary in order to substantiate their role in SCLC.

Regarding miR-based therapy, many technical hurdles which are not discussed in detail here have been identified. Issues are targeting of miRs to tumor cells, efficacy of intracellular escape, removal by the reticulo-endothelial system, excretion by the kidneys, pharmaco-kinetic and pharmaco-dynamic issues, immunogenicity, toxicity and cytokine-release syndrome (149-154). Recently, the field has experienced several set-backs, mainly due to toxicity issues (155). It remains to be seen whether miRs are tools for further target identification and whether miR-based therapy is a viable strategy for treatment of SCLC.

Conflicts of Interest

AN is and UHW was an employee of Roche.

Authors' Contributions

AN and UHW jointly designed and prepared the article.

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