CANCER GENOMICS & PROTEOMICS *19*: 372-389 (2022)
doi:10.21873/cgp.20327

Review

Long Non-coding RNAs With *In Vitro* and *In Vivo* Efficacy in Preclinical Models of Esophageal Squamous Cell Carcinoma Which Act by a Non-microRNA Sponging Mechanism

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Abstract. *Esophageal squamous cell carcinoma is a type of cancer with dismal prognosis. Surgery, chemo- and radiation therapy, as well as immune checkpoint-blocking immunotherapy lead to limited improvement of survival of patients; therapy resistance and recurrencies hamper these treatment modalities. Therefore, the identification of new targets and treatment approaches is of paramount importance. We have searched the literature and identified 7 down-regulated and 16 up-regulated non-coding RNAs, which showed efficacy in preclinical esophageal squamous cell carcinoma-related in vitro and in vivo models, and discuss their diverse mode of actions. We excluded long non-coding RNAs, which act by sponging of microRNAs. It is presently unclear whether long non-coding RNA/protein, DNA and RNA interactions can be targeted with small molecules. We describe reconstitution therapy and inhibition of the corresponding long non-coding RNAs with small interfering RNAs and antisense oligonucleotides. Also, we discuss emerging targets for treatment of esophageal squamous cell carcinoma.*

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Key Words: Antisense oligonucleotides (ASO), mode of action of long-non coding RNAs, oncogenic and tumor-suppressive lncRNAs, reconstitution and inhibition of lncRNAs, siRNA, xenografts, review.

Among cancers, esophageal cancer ranks eighth in terms of incidence and sixth in terms of mortality (1). Two subtypes have been identified: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). EAC occurs in the lower and middle part of the esophagus and derives from esophagus glandular cells near the stomach. ESCC is found in the upper part of the esophagus and originates from the esophageal squamous epithelium (2). EAC is the predominant subtype in Europe and North America, whereas ESCC is the most frequent subtype in Southeast Asia and Africa (2). Despite treatment by surgery, radiation, chemotherapy with 5-fluorouracil (5-FU) and irinotecan, and immunotherapy with monoclonal antibodies (mAbs) directed against programmed cell death protein 1 (PD1) (pembrolizumab and nivolumab), patients with EC have a dismal prognosis (3-5). Many types of therapeutic interventions such as targeting the epidermal growth factor receptor (EGFR), vascular endothelial growth factor and receptor (VEGF and VEGFR), hepatocyte growth factor (HGF)/tyrosine kinase c-MET as well as the mechanistic target of rapamycin (mTOR) pathway and epigenetic therapies are under exploration (3-5). Among the problems to be tackled are high mutational load, therapy resistance, spatial intratumoral heterogeneity and temporal clonal evolution (6-9). In this review, we focus on long non-coding RNAs (lncRNAs) with efficacy in ESCC-related preclinical *in vitro* and *in vivo* models in order to explore new treatment entities and to identify new targets for therapy of ESCC.

Role of Long Non-coding RNAs in Cancer

lncRNAs comprise more than 200 nucleotides (nts) and are transcribed by RNA pol II and III (10). More than 60,000 lncRNAs are predicted in humans (11). They are involved in cancer cell proliferation, migration, invasion, epithelial-mesenchymal transition (EMT), apoptosis and anti-tumor drug

resistance (10). lncRNAs are predominantly located in the nucleus, whereas a minority is transported to the cytoplasm (11). They can act as oncogenes as well as tumor suppressors (TS) (12-14). These effects are achieved by a multitude of functional properties, such as transcriptional regulation, post-transcriptional regulation of mRNA stability, modulation of chromatin structure and chromatin positioning by recruitment of chromatin-modifying enzymes, regulation of splicing, translation and protein stability, assembly of membrane-less nuclear bodies, self-activation of genes by natural antisense transcripts and mRNA modification (15-17). lncRNAs can modulate signaling pathways, such as AKT, NOTCH, p53, WNT/β catenin and hypoxia inducible factor 1(HIF-1) driven processes (18). Among the mechanisms involved in physiological functions of lncRNAs are sponging of microRNAs as well as physical interaction with nucleic acids, protein, and lipids *via* interactor elements (18).

Down-regulated lncRNAs and lncRNAs Involved in Signaling

lncRNA NKILA targets nuclear factor κB signaling. lncRNA NFκB interacting (NKILA) was down-regulated in ESCC samples and correlated with poor prognosis (19, 20). NKILA inhibited proliferation of Eca109 and Eca9706 ESCC cells as well as migration and invasion of Eca109, Eca9706, KYSE30 and KYSE180 ESCC cells *in vitro*. Knockdown of NKILA stimulated growth of Eca109 cells and increased lung metastases of Eca109, Eca9706 and KYSE30 cells after tail vein injection into nude mice (19, 20). It was shown that NKILA inhibited signaling of nuclear factor κB (NFκB), an inducible transcription factor. NFκB signaling is activated by phosphorylation of nuclear factor of κ light polypeptide gene enhancer in B-cells, inhibitor α (IκBα) through IκB kinase (IKK), which leads to translocation of NFκB into the nucleus. NKILA interferes directly with IκBα and blocks its phosphorylation sites leading to interruption of NFκB signaling (19-21) (Figure 1, Figure 2, Figure 3, Figure 4, and Figure 5A). Matrix metalloproteinase 14 (MMP14), a transmembrane protease which activates MMP2 and confers aggressive biological properties was identified as a downstream effector of NFκB signaling (19, 22). MMP14 mediates proliferation, migration and invasion of ESCC cells and high MMP14 correlates with poor survival (23-25). NFκB signaling plays a role in cancer formation, promotion of inflammation (26), and cancer development and progression (27). Therefore, this pathway is a target of anti-cancer drug development (28). It has been shown that targeting NFκB signaling suppresses TG, angiogenesis and metastases in preclinical models of ESCC (29).

lncRNA GASL1 targets Wnt/β-catenin signaling. Growth arrest associated lncRNA1 (GASL1) (Figure 1) was down-regulated in ESCC cell lines, induced cell-cycle arrest, inhibited cell migration and invasion *in vitro* and TG *in vivo* (30). GASL1 inactivated WNT/β-catenin signaling by inhibition of dickkopf1 (DKK1), wingless-type MMTV integration site family, member 3a (WNT3A), β-catenin and inhibited transcription factor c-MYC (Figure 1). The molecular basis of these findings is not yet resolved. WNT signaling is frequently deregulated in cancer (31, 32). WNT3a and DKK1 are associated with poor prognosis in patients with ESCC (33, 34). Involvement of DKK1 in invasive growth of ESCC cells has been reported (35). Furthermore, DKK1 is involved in maintaining stem cell-like properties of ESCC cells (36). It has been shown independently that inhibition of Wnt/β-catenin signaling results in attenuation of growth of ESCC cells (37).

lncRNA ADAMTS9-AS2 inhibits Cadherin3. ADAM metallopeptidase with thrombospondin type1 motif 9 antisense RNA 2 (ADAMTS-AS2) has been shown to be expressed at low levels in ESCC patients. ADAMTS-AS2 inhibited proliferation, migration and invasion of ESCC cells *via* down-regulation of Cadherin 3 (CDH3) (38). Over-expression of ADAMTS-AS2 in ESCC cells inhibited TG in nude mice. Down-regulation of CDH3 by ADAMTS-AS2 was achieved by recruitment of DNA methyltransferases 1 and 3 (DNMT1/DNMT3) to the CHD3 gene as shown by RNA pull-down experiments (1) (Figure 1). CDH3 belongs to the cadherin superfamily of Ca-dependent cell-cell adhesion proteins composed of five extracellular cadherin repeats, a transmembrane region and a conserved cytoplasmic tail (39). CDH3 is involved in metastasis through activation of RHO GTPases (40). CDH3 is frequently over-expressed in breast cancer and CRC, which leads to enhancement of migration, invasion and tumor aggressiveness (41, 42). In ESCC, over-expression of CDH3 has been demonstrated (43).

lncRNA IRF1-AS activates interferon response. Down-regulation of interferon-regulatory factor 1 antisense RNA (IRF1-AS) (Figure 1) predicted poor clinical outcome in ESCC patients (44). IRF1-AS inhibited proliferation and promoted apoptosis of KYSE30 and KYSE180 ESCC cells *in vitro* and *in vivo* in nude mice. Interestingly, IRF1-AS stimulated expression of its own gene by interacting with interleukin enhancer binding factor 3 (ILF3) and DExH-box helicase 9 (DHX9). Both are located in the nucleus, have RNA binding motifs and function as transcriptional co-activators (45, 46) (Figure 1 and Figure 5B). IRF1-AS activates interferon response *in vitro* and *in vivo*. IRF1 interacts with other transcription factors to stimulate or to repress specific genes in the nucleus and acts as a negative regulator of cell proliferation (47, 48). IRF1 binds to IFN specific response elements *via* an N-terminal helix-turn-helix DNA binding domain to induce the interferon response (49, 50).

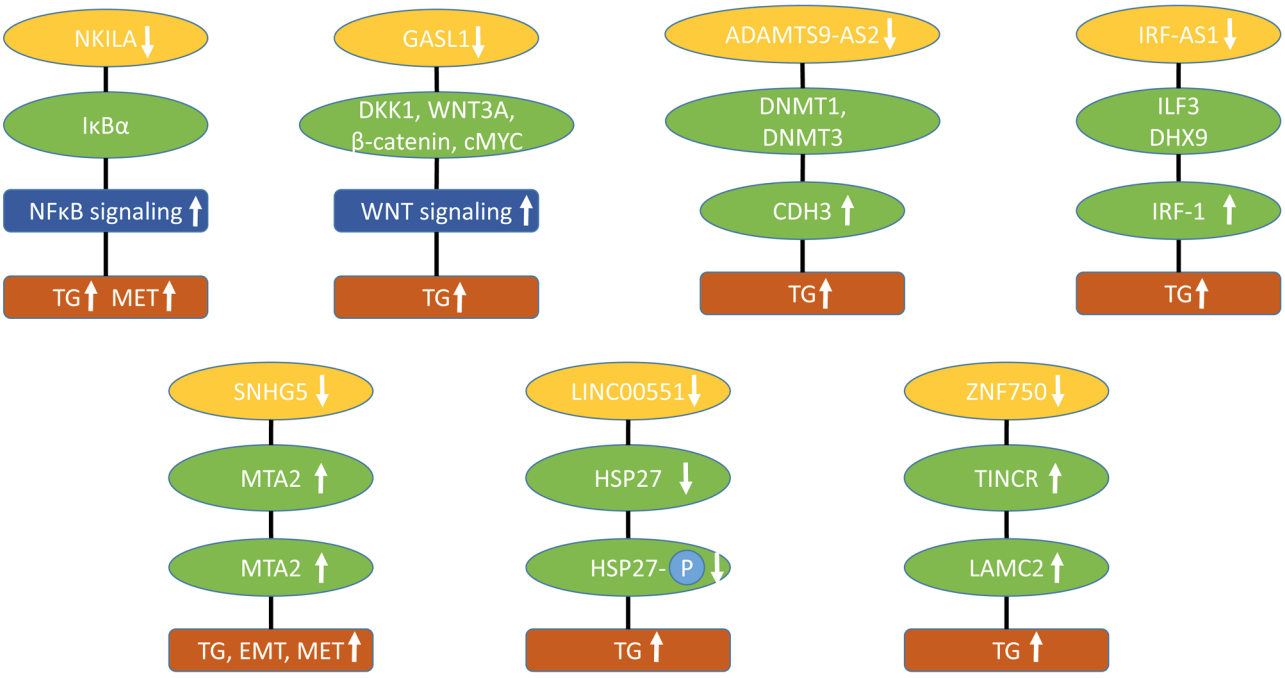

Figure 1. *Down-regulated long non-coding RNAs with efficacy in preclinical esophageal squamous cell carcinoma related in vitro and in vivo models. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. ADAMTS9-AS2: ADAM metalloproteinase with thrombospondin type 9 motif antisense RNA2; DHX9: DExH-box helicase 9; DKK1: dickkopf-related protein 1; DNMT1,3: DNA methyltransferase 1,3; EMT: epithelial-mesenchymal transition; ILF3: interleukin enhancer binding factor 3; GASL1: growth-arrest-associated long non-coding RNA1; HSP27: heat shock protein 27; IκBα: nuclear factor κB inhibitor α; IRF1: interferon regulatory factor 1; IRF1- AS: interferon regulatory factor 1- antisense RNA; LAMC2: laminin γ2; LINC 0051: long intergenic non-protein coding RNA 0051; MET: metastasis; MTA2: metastasis-associated 2; c-MYC: transcription factor c-MYC; NFκB: nuclear factor κB; NKILA: NFκB interacting lncRNA; SNHG5: small nucleolar RNA host gene 5; TG: tumor growth; TINCR: terminal differentiation inducing non protein coding RNA; WNT3A: wingless-type MMTV integration site family, member 3A; ZNF 750: zinc finger 750.*

lncRNA SNHG5 targets metastasis-associated 2 protein. Small nucleolar RNA host gene 5 (SNHG5) (Figure 1) has been shown to be down-regulated in ESCC tissues and cell lines and correlated with cancer progression and survival (51). Over-expression of SNHG5 inhibited proliferation, migration and invasion of ESCC cells *in vitro* and *in vivo*. SNHG5 reversed EMT and was shown to directly interact with metastasis-associated 2 (MTA2). SNHG5 down-regulated MTA2 at the transcriptional level and caused ubiquitin-mediated degradation of MTA2 (Figure 1 and Figure 5C). The latter is a regulator of nucleosome remodeling and histone deacetylation complex and also functions as a hub for cytoskeleton organization and transcription (52). The MTA family consists of three members, MTA1, MTA2 and MTA3 and expression of MTA2 correlates with aggressive phenotype and invasiveness of several types of tumors (53, 54). MTA2 has been shown to promote metastasis of ESCC (55).

lncRNA LINC00551 targets heat shock protein 27. Long intergenic non-protein coding RNA 00551(LINC 00551) (Figure 1) has been shown to be down-regulated in ESCC tissues and correlated with poor survival (56). LINC 00551 over-expression inhibited ESCC cell proliferation and invasion, whereas its knockdown promoted ESCC proliferation *in vitro* and *in vivo*. LINC 00551 was found to bind to heat shock protein 27 (HSP27) and decreased its phosphorylation. Heat shock proteins are regulators of proliferation, survival and apoptosis of cancer cells by their involvement in protein folding and maturation protecting them from degradation (57). HSP27 activates WNT/β-catenin signaling, the hippo pathway and oncogenic and metastatic pathways *via* transforming growth factor β (TGF-β)/SMAD signaling (58). In ESCC, expression of HSP27 correlates with lymph node metastasis and regulates pyruvate kinase isoenzyme M2 to promote ESCC progression (59). Several heat shock protein inhibitors for treatment of cancer have been identified, however, they showed limited efficacy in clinical studies due to toxicity issues and activation of heat shock factor-1 (HSF-1) leading to protective heat-shock responses (60, 61).

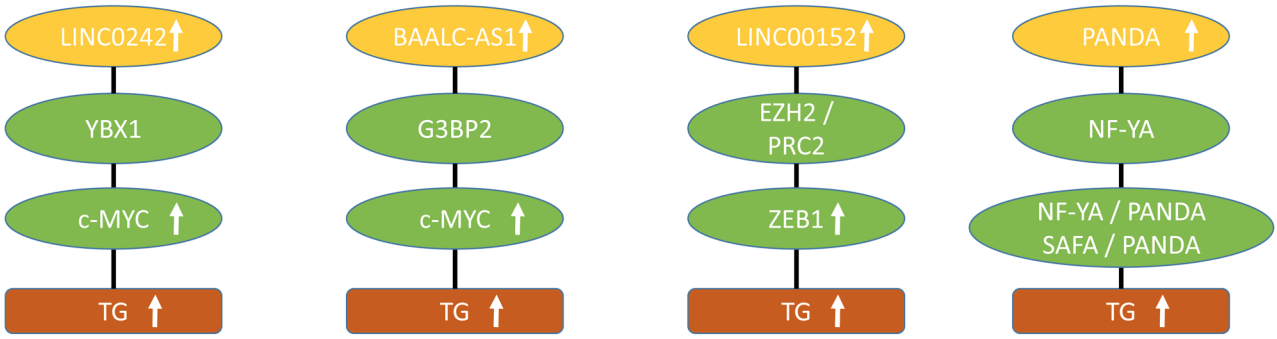

Figure 2. *Upregulated long non-coding RNAs mediating increase of transcription factors with efficacy in preclinical esophageal squamous cell carcinoma related in vitro and in vivo models. Upward arrows indicate upregulation, downward arrows indicate down-regulation. BAALC-AS1: BAALC-antisense 1; c-MYC: transcription factor c-MYC; EZH2: enhancer of zeste homolog 2; G3BP2: GAPSH3 domain binding protein 2; LINC00152: long intergenic non-coding RNA 00152; LINC02042: long intergenic non-protein coding RNA 2042; NF-YA: nuclear transcription factor Y-subunit α; PANDA: p21 nuclear RNA DNA damage activated lncRNA; SAFA: scaffold attachment factor A; TG: tumor growth; YB1: Y-box binding protein 1; ZEB1: zinc finger e-box binding homeobox 1.*

lncRNA ZNF750 targets Laminin γ2. lncRNA zinc finger 750 (ZNF750) (Figure 1) has been shown to be under-expressed in ESCC tissues in comparison to corresponding normal tissues (62). ZNF750 inhibited migration of ESCC, induced epidermal differentiation of ESCC cells and attenuated growth of UMSCC1 ESCC derived xenografts in immuno-compromised mice. ZNF750 mediated transcription of terminal differentiation inducing non-coding RNA (TINCR), a potential biomarker and therapeutic target for cancer (62, 63). In addition, ZNF750 repressed laminin γ2 (LAMC2) at the transcriptional level (62). Laminins are secreted components of the extracellular matrix, which are composed of three non-identical chains (α, β and γ). Laminins regulate cell adhesion, differentiation, migration and metastases (64). Over-expression of LAMC2 predicts poor prognosis in colorectal cancer (CRC) patients and promotes proliferation, migration and invasion (65). Also, in ESCC, expression of LAMC2 is associated with recurrence and poor prognosis (66).

Up-regulated lncRNAs and lncRNAs Activating Transcription Factors

Linc 02042 targets c-MYC. Long intergenic non-protein coding RNA 2042 (LINC 02042) (Figure 2 and Figure 6A) has been shown to be up-regulated in ESCC (67). It inhibited proliferation, migration and invasion of KYSE30 and KYSE150 ESCC cells *in vitro* and TG of KYSE30 cells *in vivo* in nude mice. LINC 02042 stabilized c-MYC mRNA by binding to LINC 02402-Y box binding protein 1 (YBX1) complex of the 3´- untranslated region (UTR) of c-MYC (67). A positive feedback loop was implemented by transactivation of LINC 02042 by c-MYC (67). YBX1 is a multi-functional protein that can modulate RNA stability by binding to AU-rich elements on the 3´-UTR of mRNAs (68, 69). c-MYC is a nuclear transcription factor, which is frequently deregulated in cancer mediating proliferation, invasion, metastasis, cell growth, ribosome biogenesis and metabolism of cancer cells (70-74). However, due to its ubiquitous expression and its disordered structure, druggability of c-MYC is still unclear.

BAALC-AS1 targets c-MYC. lncRNA BAALC antisense RNA 1 (BAALC-AS1) (Figure 2 and Figure 6A) has been shown to be up-regulated in ESCC and correlated with poor prognosis (75). It promoted proliferation, migration, colony formation and viability of KYSE 450 and -510 ESCC cells and TG of their xenografts in nude mice. These effects were found to be due to the stabilization of c-MYC. BAALC-AS1 released RAS GAPSH3 domain-binding protein 2 (G3BP2) from c-MYC mRNA by direct binding and thereby inhibited the degradation of c-MYC RNA 3'-UTR by G3BP2. The latter has RNA binding sites and affects mRNA stability of c-MYC (76, 77). A positive forward loop was implemented by stimulation of BAALC-AS1 by c-MYC (75). In ESCC, expression of G3BP2 is related to lymph node metastasis and prognosis (78).

Linc 00152 up-regulates zinc finger e-box binding homeobox 1. Long intergenic non-coding RNA (LINC 00152) (Figure 2 and Figure 6B) has been shown to be highly expressed in ESCC tissues and enhanced oxaliplatin resistance of ESCC cells (79). Down-regulation of LINC 00152 inhibited EMT and resistance to oxaliplatin in KYSE150 and TE-1 ESCC cells. In nude mice, LINC 00152 promoted TG of KYSE 150 xenografts after subcutaneous implantation. These effects were

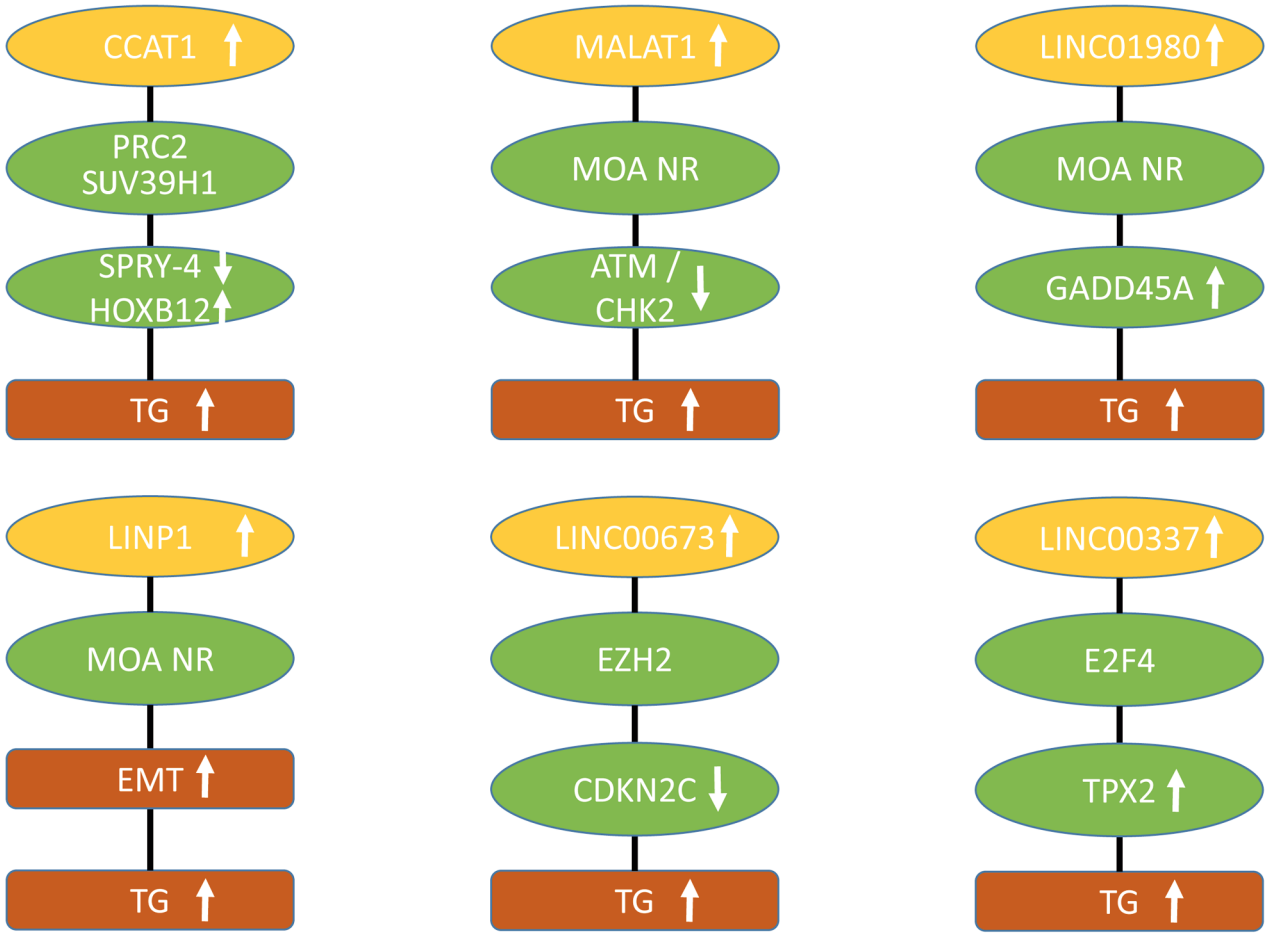

Figure 3. *Up-regulated long non-coding RNAs mediating modulation of signaling and cell-cycle related targets with efficacy in preclinical esophageal squamous cell carcinoma in vitro and in vivo models. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. ATM: Ataxia telangiectasia mutated; CCAT1: lncRNA colon cancer-associated transcript 1; CDKN2C: cyclin-dependent kinase 4 inhibitor C; CHK2: checkpoint kinase 2; E2F4: transcription factor E2F4; EZH2: enhancer of zeste homolog 2; EED: polycomb protein EED; EMT: epithelial mesenchymal transition; GADD45A: growth arrest and DNA inducible 45A; HOXB13: homeobox transcription factor B13; LINC00337: long intergenic non-protein coding RNA 00337; MALAT1: metastasis associated lung adenocarcinoma transcript 1; LINC00673: long intergenic non-protein coding RNA 00673; LINC01980: long intergenic non-protein coding RNA 1980; LINP1: lncRNA in non-homologous end joining pathway; MOA NR: mode of action not resolved; PRC2: polycomb repressive complex 2; SPRY4: sprouty homolog 4; SUV39H1: histone-lysine-N-methyltransferase; SUZ12: polycomb protein SUZ12; TG: tumor growth; TPX2: targeting protein for xlp2.*

mediated by up-regulation of transcription factor zinc finger e-box binding homeobox 1 (ZEB1). The latter has been shown to be involved in invasion and metastasis of ESCC (80). LINC 00152 released enhancer of zeste homolog 2 (EZH2) from the ZEB1 gene by binding to the polycomb repressive complex 2 (PRC2), thus reducing trimethylation of lys 27 in histone 3 and promoting expression of ZEB1. EZH2 is a histone-lysine N-methyltransferase which facilitates heterochromatin formation and promotes tumorigenesis (81). EZH2 inhibitor Tazemetostat has been recently approved for the indication epithelioid sarcoma (82). EZH2 expression correlates with aggressiveness and prognosis of ESCC (83).

lncRNA PANDA interacts with nuclear transcription factor Y, subunit α and nuclear matrix protein scaffold attachment factor A. High expression of p21-associated nuclear RNA DNA damage activated (PANDA) (Figure 2 and Figure 6C) has been shown to be associated with advanced clinical stage and shorter overall survival in ESCC patients (84). Down-regulation of PANDA suppressed ESCC cell proliferation and colony formation, arrested G1/S transition *in vitro* and development of tumors *in vivo* in nude mice. Depletion of PANDA reduced expression levels of E2F1, cyclins D1, D2 and E, and BCL2. The reduction in the expression of these cell-cycle regulators and anti-apoptotic genes was due to binding of nuclear

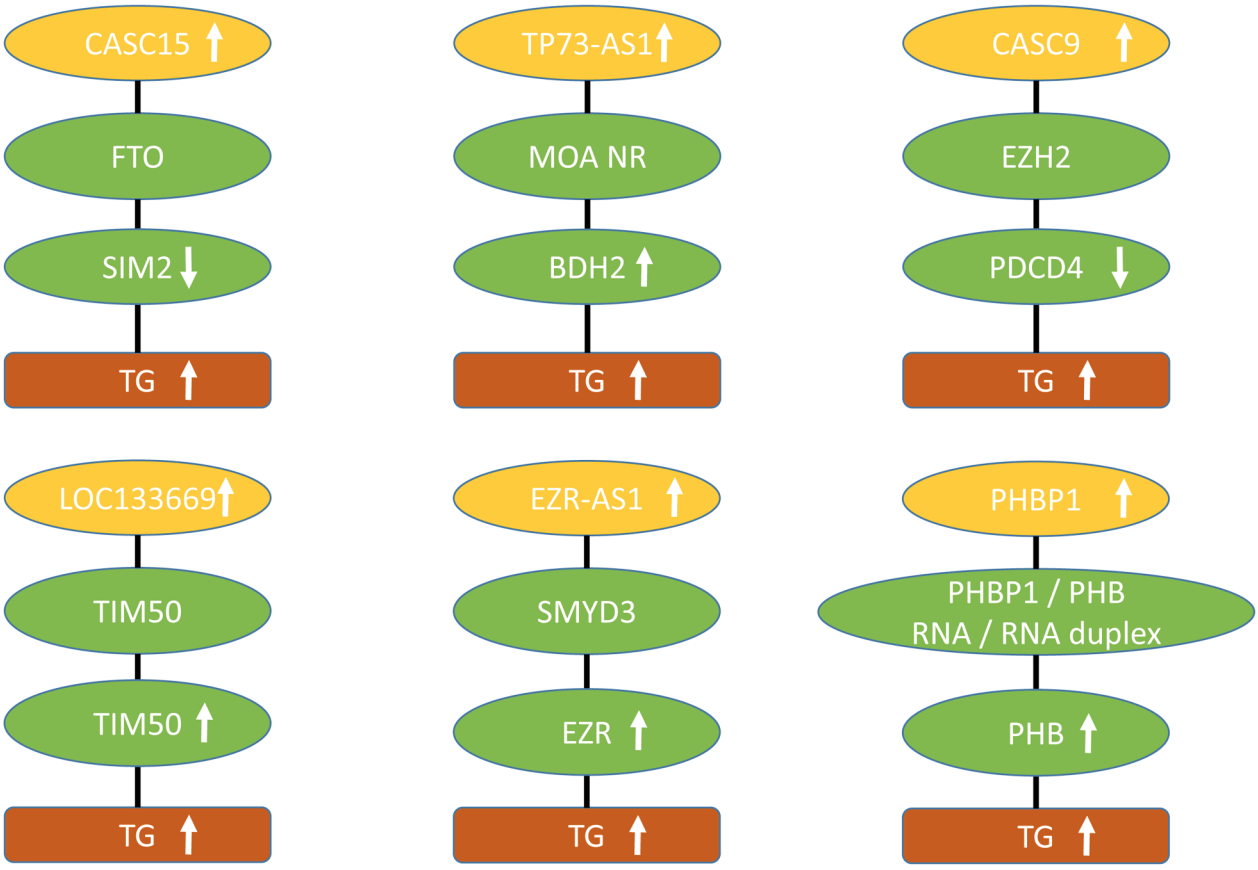

Figure 4. *Up-regulated long non-coding RNAs mediating modulation of additional targets with efficacy in preclinical esophageal squamous cell carcinoma related in vitro and in vivo models. Upward arrows indicate up-regulation, downward arrows indicate down-regulation. BDH2: 3-Hydroxybutyrate dehydrogenase type 2; CASC9: lncRNA cancer susceptibility 9; CASC15: lncRNA cancer susceptibility 15; EZH2: enhancer of zeste homolog 2; EZR: ezrin; EZR-AS1: ezrin-antisense 1 lncRNA; FTO: fat mass and obesity associated protein; LOC 100133669: long non-coding RNA 100133669; MOA-NR: mode of action not resolved; PDCD4: programmed cell death 4; PHB: prohibitin; PHBP1: prohibitin pseudogene 1; SIM2: single-minded 2; SMYD3: SET- and MTN-domain containing 3; TG: tumor growth; TIM50: mitochondrial inner membrane translocase subunit 50; TP73-AS1: TP73 antisense RNA1.*

transcription factor Y, subunit α (NF-YA) to PANDA. NFYA consists of three subunits, regulatory subunit NF-YA and subunits NF-YB and NF-YC, which bind to CCAAT motifs on DNA. NF-YA drives a plethora of cell-cycle regulatory genes and acts as a key player in the regulation of proliferation of cancer cells (85, 86). In addition, PANDA bound to nuclear matrix protein scaffold attachment factor A (SAFA) to switch the tumor proliferation program through CyclinD1/2-Cyclin E1 and BCL2 pathways. SAFA can bind to DNA, RNA and non-coding RNA such as PANDA (87, 88).

lncRNAs Targeting Cell-cycle and Signaling Related Components

lncRNA CCAT1 targets sprouty homolog 4 and homeobox transcription factor B13. lncRNA colon cancer associated transcript 1 (CCAT1) (Figure 3 and Figure 6D) has been shown to be up-regulated in ESCC tissues and correlated with poor prognosis (89). Knockdown of CCAT1 in Eca-109 and TE-1 ESCC cells inhibited cell proliferation and migration *in vitro*. CCAT1 also regulated proliferation and migration of Eca-109 xenografts in nude mice. From a mechanistic point of view, CCAT leads to down-regulation of sprouty homolog 4 (SPRY4) and up-regulation of homeobox transcription factor HOXB13 (90, 91). SPRY4 is an inhibitor of transmembrane tyrosine kinase receptor transduced mitogen-activated protein kinase (MAPK) signaling (90). The other target, HOXB13, acts as an oncogenic transcription factor (91). Inhibition of expression of SPRY4 was achieved by recruitment of PRC2 and SUV39H1 by interaction with CCAT1 (89). PRC2 is a histone methyltransferase composed of catalytic subunit

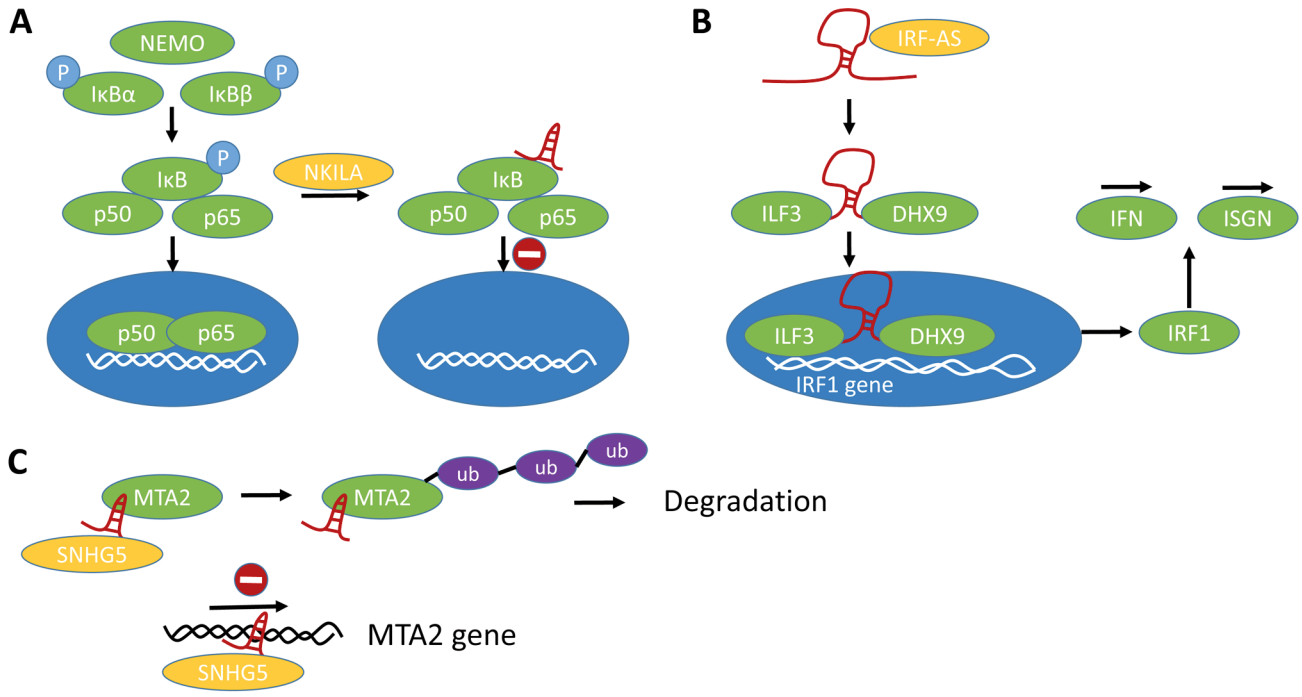

Figure 5. *Mode of action of selected down-regulated long non-coding RNAs. A) NKILA inhibits phosphorylation of IκB and subsequent translocation of transcription factors p50 and p65 into the nucleus. B) IRF1-AS1 stimulates transcription of interferon and interferon-stimulated genes by interaction with co-factors and enhances expression of its own gene. C) lncRNA SNHG5 promotes degradation of MTA2 and inhibits expression of the MTA2 gene. Corresponding lncRNAs are shown by red hair-pin structures. DHX9: DExH-box helicase 9; GASL1: growth arrest associated lncRNA; IκB: nuclear factor of κ light chain polypeptide gene enhancer in B cells inhibitor; IKKα,β: inhibitor of nuclear factor κB kinase subunit α or β; IRF1: interferon regulatory factor 1; IRF-AS1: interferon-regulatory factor 1 antisense RNA1; IKKα,β: IκB kinase α,β; ISGs: interferon-stimulated genes; ILF3: interleukin enhancer binding factor 3 (ILF3); MTA2: metastasis associated 2; NEMO: NFκB essential modulator; NKILA: NFκB interacting lncRNA; p50: NFκB1; p65: NFκB2; ub: ubiquitin; SNHG5: small nucleolar RNA host gene 5 lncRNA; ub: ubiquitinylation.*

EZH2 and polycomb proteins SUZ12 and EED (92-94) resulting in tri-methylating histone H3 Lys 27, which is a repressor of transcription. SUV39H1 also acts as a histone methyltransferase and a transcriptional repressor by histone H3 lysine 9 trimethylation (95). These interactions occurred in the nucleus. In addition, HOXB13 was upregulated by CCAT1 due to sponging of miR-7 in the cytoplasm which facilitates growth and migration of ESCC cells (96).

lncRNA MALAT1 targets the ataxia telangiectasia mutated-checkpoint kinase 2 pathway. Metastasis associated lung adenocarcinoma transcript 1 (MALAT1) (Figure 3) has been shown to be up-regulated in advanced ESCC tissues (97). Knockdown of MALAT1 decreased growth and invasion of EC109 and EC9706 ESCC cells *in vitro* and growth of xenografts *in vivo* after subcutaneous implantation into nude mice. Knockdown of MALAT1 induced cell-cycle arrest by activation of the Ser-Thr kinase ataxia telangiectasia mutated (ATM)-checkpoint kinase 2 (CHK2) pathway. Conversely, high expression of MALAT1 promoted ESCC proliferation by dephosphorylation and inhibition of the ATM/CHK2 pathway. ATM is a mediator of DNA repair, is recruited to DNA double-strand breaks and subsequently phosphorylates CHK2 (98-100). The latter plays an important role in cancer development and cell checkpoint control of cancer (101, 102). Mechanistic details of inhibition of ATM/CHK2 by MALAT are not yet resolved.

lncRNA LINC01980 up-regulates growth arrest and DNA-inducible 45A. LINCO1980 has been shown to be up-regulated in ESCC and correlated with poor prognosis (103). It promoted ESCC growth *in vitro* and *in vivo*, accelerated cell-cycle progression and prevented apoptosis. Growth arrest and DNA-inducible 45A (GADD45A) was identified as a possible target of LINCO1980 based on micro-array analysis. GADD45A promoted ESCC growth and LINC01980 up-regulated GADD45A. GADD family of proteins consist of three 18 Kd members, which are localized in the nucleus and the cytoplasm (104). Each of the GADD45 gene products has both TS and tumor promoting functions dependent on the cell type, tissue and transforming event (105, 106). GADD45A can induce cell-cycle arrest,

apoptosis and DNA repair; however, tumor-promoting activities of GADD45A have also been reported (105, 106). GADD45A has been shown to be over-expressed in CRC and pancreatic cancer (107, 108). The molecular mechanisms underlying up-regulation of GADD45A by LINCO1980 have not been resolved. GADD45A does not seem to be a high priority target for the treatment of ESCC based on the limited data presently available.

lncRNA LINP1 induces epithelial-mesenchymal transition. High expression of intergenic lncRNA in the non-homologous end joining pathway 1 (LINP1) correlated with poor prognosis in patients with ESCC (109). Knock-down of LINP1 promoted cell-cycle arrest at G2/M and apoptosis, and inhibited EMT in EC907 ESCCs *in vitro*. *In vivo*, knockdown of LINP1 mediated inhibition of TG of EC907 xenografts in nude mice. Suppression of EMT was mediated by down-regulation of N-cadherin, vimentin, snail and slug. The mechanistic details underlying these effects were not resolved. EMT is a cell biological program with a series of phenotypic states and is involved in invasiveness and metastasis. Also, intermediate cell types between the epithelial and mesenchymal cell state play a role in this process (110-112). In breast cancer, it has been shown that LINP1 acts as an oncogene (113).

lncRNA LINC00673 down-regulates cyclin-dependent kinase 2 inhibitor C. Up-regulation of long intergenic non-protein coding RNA 00673 (LINC00673) (Figure 3 and Figure 6E) correlated with poor prognosis in ESCC patients (114). In KYSE30 and KYSE510 ESCC cells, knockdown of LINC00673 inhibited proliferation and cell-cycle arrest at the G1/S checkpoint *in vitro* and reduced TG *in vivo* in nude mice. It was found that LINC00673 inhibited expression of cyclin-dependent kinase 2 inhibitor C (CDKN2C) through recruitment of EZH2 to the promoter region of CDKN2C generating H3K27me3, which inhibited gene expression (114). CDKN2C interacts with cyclin-dependent kinases 4 and 6 (CDK4/6) and prevents their activation (115, 116). Three CDK4/6 inhibitors have been approved for treatment of hormone receptor+/HER2+ breast cancer: palbociclib, ribociclib and abemaciclib (117, 118). Ongoing clinical studies in other types of solid tumors including ESCC have been reported (119). Limited activity has been shown in palbociclib treated patients with advanced esophageal or gastric cancer in Phase II clinical studies (120).

lncRNA LINC00337 up-regulates targeting protein for xlp2. Long intergenic non-protein coding RNA 00337 (LINC00337) (Figure 3) has been shown to be up-regulated in ESCC and corresponding cell lines (121). Down-regulation of LINC00337 suppressed autophagy and enhanced chemosensitivity to cisplatin. In nude mice, down-regulation of LINC00337 led to aggravated growth of Eca109 ESCC xenografts after subcutaneous implantation (121). LINC00337 interacted with transcription factor E2F4, which mediated transcription of the targeting protein for xlp2 (TPX2) (121). E2F4 is involved in controlling the cell-cycle (122). TPX2 functions as a spindle and microtubule assembly factor and regulates cell growth during M-phase and its expression correlates with progression of tumors (123, 124). TPX2 recruits and activates aurora kinase A (AURKA) (125). Several AURKA inhibitors are under clinical investigation (126). In ESCC, TPX2 mediates proliferation, invasion and metastasis and is associated with poor clinical outcome (127-129).

lncRNAs Targeting Further Components

CASC15 targets single-minded 2. lncRNA cancer susceptibility candidate 15 (CASC15) (Figure 4 and Figure 6F) has been shown to be increased in ESSC tissues (130). CASC15 knockdown decreased proliferation and promoted apoptosis in Eca109 and KYSE450 ESCC cells *in vitro*. Silencing of CASC15 inhibited growth of KYSE450 xenografts in nude mice. CASC15 attenuated expression of transcription factor single-minded 2 (SIM2) and decreased stability of SIM2 mRNA *via* fat mass and obesity associated protein (FTO). It has been shown that SIM2 can suppress EMT in ESCC (131). FTO is a α-keto glutamate-dependent dioxygenase, which mediates oxidative demethylation of different RNA species affecting their splicing and stability (132, 133). FTO regulates acute myeloid leukemia (AML) by targeting 3′UTR of ankyrin repeat and SOCS box containing 2 and retinoic acid α transcripts (134). In ESSC, FTO has been shown to promote proliferation and migration through up-regulation of MMP13 (135).

Lnc TP73-AS1 up-regulates type2-hydroxybutyrate dehydrogenase. TP73-AS1 has been shown to be up-regulated in ESCC and its knockout inhibited proliferation and induction of apoptosis in EC9706 and KYSE30 ESCC cells *in vitro* (136) (Figure 4). siRNA directed against TP73-AS1 attenuated proliferation of EC9706 and KYSE30 cells *in vivo*. Knockdown of TP73-AS1 inhibited cytosolic 3-hydroxybutyrate dehydrogenase type 2 (BDH2). Knockdown of the latter attenuated proliferation and induced apoptosis of EC9706 and KYSE30 cells. BDH2 over-expression partially rescued proliferation and suppressed apoptosis in lncRNA TP73-AS1 knockdown cells. BDH2 plays a role in utilization of ketone bodies in mitochondria and the tricarboxylic acid cycle (137). Furthermore, BDH2 functions as an anti-apoptotic factor through survivin (138). However, the function of BDH2 seems to be context-dependent, because it functions as a TS in gastric cancer and hepatocellular carcinoma (139, 140).

lncRNA Casc9 down-regulates programmed cell death 4. Lnc RNA cancer susceptibility 9 (CASC9) up-regulation

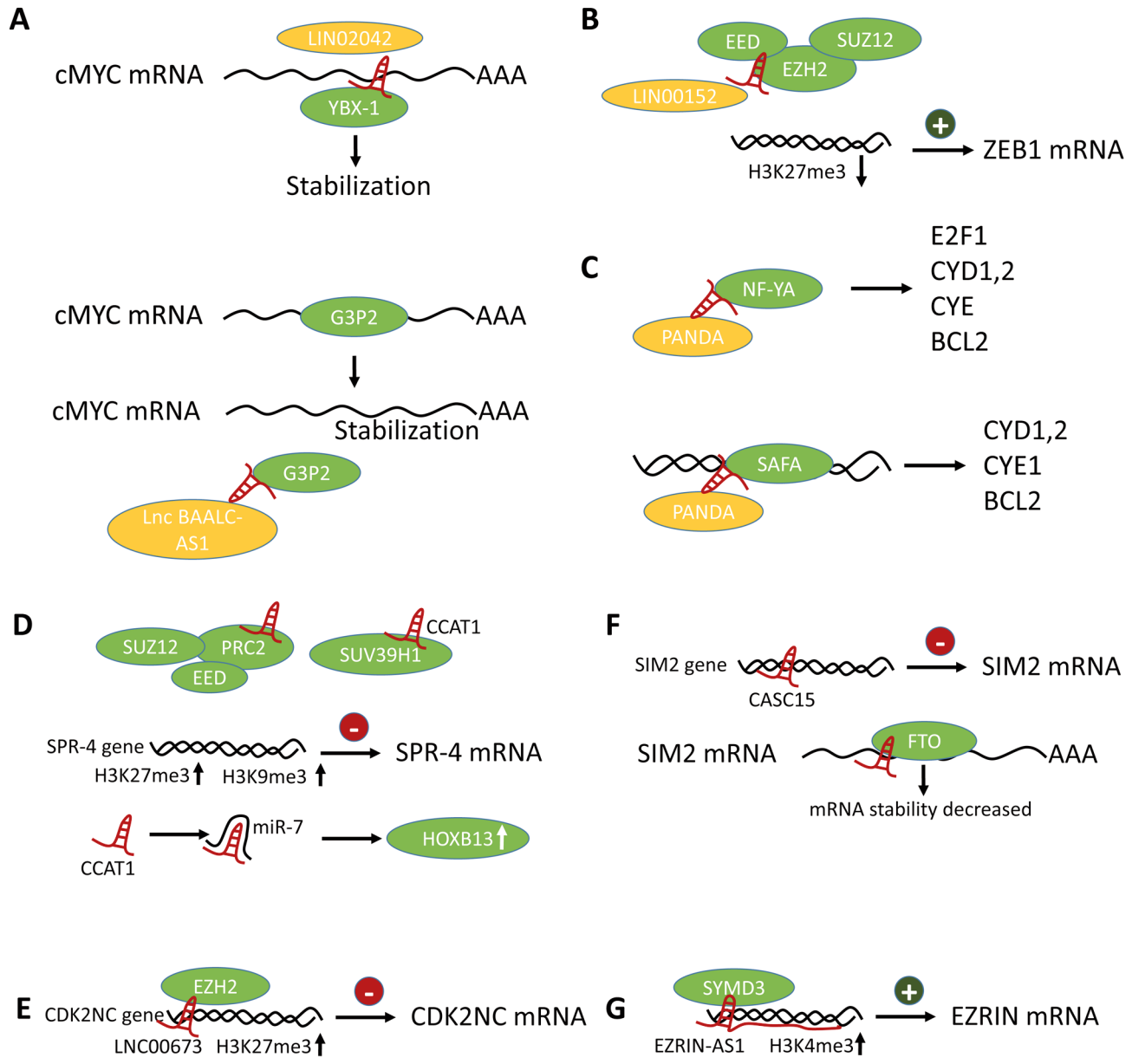

Figure 6. *Mode of action of selected up-regulated long non-coding RNAs. A) LINC 02042 and lnc BAALC-AS1 stabilize c-MYC mRNA. LINC 02042 stabilizes c-MYC mRNA by recruiting YBX-1 to its 3´-UTR. Lnc BBALB-AS1 releases G3P2 from the 3´-UTR of c-MYC mRNA through direct binding of G3P2 resulting in stabilization of c-MYC mRNA. B) Lin00152 binds to the PCR2 complex and inhibits its interaction with the promoter region of the ZEB1 gene resulting in down-regulation of H3K27me3 and up-regulation of expression of ZEB1 mRNA. C) lncRNA PANDA releases NF-YA from the promoters of target genes and facilitates transcription by interaction with SAFA of the promoter region of selected genes. D) lncRNA CCAT1 recruits PRC2 and SUV39H1 to the SPRY-4 gene and sponges miR-7. Up-regulation of H3K27me3 and H3K9me3 leads to decreased expression of the SPRY-4 gene and sponging of miR-7 to increase of expression of HOXB13 respectively. E) Lnc00673 recruits EZH2 to the promoter of the CDK2NC gene. Increase in H3K27me3 decreases transcription of the CDK2NC gene. F) CASC15 inhibits transcription of SIM2 and decreases the stability of its mRNA by interaction with FTO in the 3´-UTR of SIM2. G) An antisense lncRNA leads to increased expression of its gene. Ezrin-AS1 recruits SYMD3 to the promoter region of the ezrin gene resulting in up-regulation of H3K4me3 and increases transcription of the ezrin gene. CCAT1: Colon cancer associated transcript1 lncRNA; CASC15: cancer susceptibility candidate 15 lncRNA; CDKN2C: cyclin-dependent kinase 4 inhibitor C; EZR-AS1: ezrin-antisense 1; EZH2: enhancer of zeste repressive complex 2 subunit; FTO: fat mass and obesity associated; HOXB13: homeobox transcription factor B13; Lin00152: long-intergenic non-coding RNA 00152; LINC 02042: long intergenic non-protein coding RNA 02042; lnc BAALC-AS1: lnc BAALC antisense RNA1; lncRNA00673: long intergenic non-protein encoding RNA00673; miR-7: microRNA 7; NF-YA: nuclear transcription factor, subunit α; PANDA: lncRNA p21-associated nuclear RNA DNA damage activated; PRC2: polycomb repressive complex 2; SAFA: scaffold attachment factor A; SIM2: single-minded 2; SUV39H1: histone methyltransferase SUV39H1; SYMD3: SET and MYND domain containing protein 3; SPRY-4: sprouty homolg 4; UTR: untranslated region; YBX1: Y-box binding protein 1; ZEB1: zinc finger E-box binding homeobox 1.*

predicted poor prognosis in ESCC (141) (Figure 4). Knockdown of Casc9 in KYSE150 and KYSE450 ESCC cells inhibited cell growth *in vitro* and *in vivo*. CASC9 promoted ESCC cell growth by negatively regulating programmed cell death 4 (PDCD4). CASC9 recruited EZH2 to the promoter of PDCD4 and increases H3K27me3, which inhibits transcription (141). PDCD4 acts as a TS, is up-regulated after initiation of apoptosis and inhibits translation (142-144). In ESCC cells, PDCD4 induces apoptosis, suppresses proliferation and inhibits AKT (145, 146).

lncRNA LOC100133669 targets mitochondrial inner membrane translocase subunit 50. Lnc RNA100133669 (LOC100133669) (Figure 4) has been shown to be up-regulated in ESCC tissues and correlated with poor prognosis (147). In KYSE150 and KYSE510 ESCC cell lines, LOC100133669 promoted proliferation and accelerated entry of cells from G2/M phase to G0/G1 phase. *In vivo*, TG is reduced in KYSE150 cells with knockdown of LOC100133669 after subcutaneous implantation into nude mice. LOC100133669 interacts with mitochondrial inner membrane translocase subunit 50 (TIM50) and inhibits its degradation by interfering with ubiquitinylation. TIM50 functions as a subunit of the TIM23 complex which is essential for directing preproteins into mitochondria (148-150). TIM50 also is involved in energy production, metabolism, cell death, cell signaling and oxidative stress (151). TIM50 also has been shown to mediate NSCLC proliferation and invasion *via* the extracellular regulated kinase (ERK) pathway (152).

lncRNA EZR-AS1 up-regulates ezrin. EZR-AS1 up-regulated ezrin (EZR) expression in KYSE150 ESCCs to promote migration *in vitro* (153) (Figure 4 and Figure 6G). *In vivo*, silencing of EZR-AS1 reduced TG of KYSE150 xenografts in nude mice. Lnc RNA EZR-AS1 formed a complex with RNA Pol II and recruited H3 lysine 4 (H3K4) methyltransferase SET- and MTN-domain containing 3 (SMYD3) to a binding site present in a GC region downstream of the EZR promoter resulting in local enrichment of H3K4me3 leading to enhanced expression of EZR (153). Ezrin/radixin/moesin (ERM) proteins function as general cross-linkers between plasma membrane proteins and the cytoskeleton and play a role in functional expression of membrane proteins on the cell surface (154). EZR mediates invasion and metastases in the process of tumorigenesis (155). In ESCC, EZR promotes growth and invasiveness and predicts a poor prognosis (156, 157). SMYD3 methylates various histone and non-histone targets and plays an oncogenic role (158). In ESSC patients, expression of SYMD3 is negatively correlated with survival time (159).

lncRNA PHBP1 increases expression of prohibitin. Prohibitin pseudogene PHBP1 (Figure 4) has been shown to be over-expressed in human ESCC tissues (160). Knockdown of PHBP1 inhibited proliferation and colony formation *in vitro* in Eca9706 and TE-1 ESCC cells. In nude mice, TG of Eca9706 and TE-1 xenografts after knockdown of PHBP1 was found. mRNA stability of prohibitin (PHB) was increased by PHBP1 through PHBP1/PHB RNA-RNA duplex formation. This indicates that the mRNA of a pseudogene, a natural antisense transcript, can stabilize the mRNA of its cognate gene and lead to increased expression of its gene product. PHB is a protein of the inner mitochondrial membrane, which is involved in cancer cell proliferation, apoptosis and metastasis (161, 162). PHB can modulate transcription by interacting with transcription factors including nuclear receptors directly or indirectly (163, 164). In ESCC, increased expression of PHB correlates with poor prognosis (165). In pancreatic cancer, PHB has been identified as a prognostic marker for worse prognosis (166). However, proapoptotic functions of prohibitin have also been reported, indicating context-dependent function (162).

Technical Issues

We have identified 7 down- and 16 up-regulated lncRNAs showing efficacy in ESCC-related preclinical *in vitro* and *in vivo* models. Down-regulated lncRNAs can be reconstituted by expression of the corresponding lncRNAs with plasmid or retroviral vectors (167). Up-regulation of the corresponding targets with small molecules is limited by issues of specificity.

In case of up-regulated lncRNAs, inhibition with siRNA and shRNA (both of them double-stranded) or antisense oligonucleotides (ASO) (single-stranded) are also options (168). siRNA or shRNA delivered into cells initiate degradation of complementary RNAs (169). Binding of ASO to their targets induces RNAseH-dependent endonucleolytic cleavage of target RNA (170). Their therapeutic applications have been optimized by introducing chemical modifications leading to phosphothioates, generation of gapmers, locked nucleic acids, morpholino oligonucleotides and peptide nucleic acids (168). Also, modulation of lncRNAs by clustered regularly interspersed short palindromic sequences-crispr associated proteins (CRISPR-CAS) based intervention is a future option (168). lncRNAs fold into complex secondary and tertiary structures and interact with DNA, RNA and proteins (171, 172). It remains to be seen whether some of these interactions can be targeted with small molecules. Proof-of-concept experiments have shown that a stabilizing triple helix in MALAT-1 can be targeted with small molecules (173).

However, major hurdles for the approaches described above have been identified. These include immunogenicity of the identified agents, specificity and delivery issues, which are not discussed in detail in this review (174). Delivery has been improved by conjugation of lncRNAs to antibodies, cell-penetrating peptides and metal nanoparticles (174).

Thus far, 11 RNA therapeutics that down-regulate genes or interfere with pre-mRNA splicing have been approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA) (174). None of them has been used in the treatment of patients with cancer. However, four cancer-related approaches are in Phase II/III clinical studies such as an siRNA targeting G12D mutated KRAS and three ASOs targeting growth factor receptor-bound protein 2 (GRB2), signal transducer and activator of transcription 3 (STAT3) and heat shock protein 27 (HSP27) (174).

Conclusion

Down-regulated lncRNAs NKILA, GASL1, ADAMTS9-AS2, IRF-AS1, SNHG5, LINC00551, and ZNF750 are candidates for reconstitution therapy. Inhibition of signaling pathways such as NFκB (IκBα), WNT and IRF1, HSP27, DNMT1/3, MTA2 and CDH3 emerge as further options to be validated in more detail.

LINC02042, BAALC-AS1, LINC00152, and PANDA are up-regulated and target transcription factors such as c-MYC, NFYA, and SAFA. Due to issues of druggability, the targeting of transcription factors is problematic (175-177) but recent developments in the field of proteolysis targeting chimera (PROTACS) might lead to breakthroughs in this field. PROTACS consist of two covalently linked modules, one binding to the target protein, the other one recruiting ubiquitin ligase mediating intracellular proteolysis of the target protein (178-181).

Up-regulated lncRNAs CCAT1, MALAT1, LINC01980, LINP1, LINC00673, and LINC00337 target signaling and cell-cycle related entities. Up-regulation of CDKN2C by inhibition of EZH2 and up-regulation of SPRY-4 by inhibition of PRC2 and SUV39H1 emerge as therapeutic options.

CASC15, TP73-AS1, and CASC9 target further components, not covered by the previously discussed categories. Inhibition of the metabolic enzyme BDH2 (182) by small molecules might be an interesting option, but validation of this target in more detail is necessary. Inhibition of EZH2 to down-regulate PDCD4 might emerge as another approach for treatment of ESCC. Inhibition of TIM50 and Ezrin might be limited by specificity and druggability issues. The role of prohibitin in ESCC merits further investigation.

It is unclear, whether interactions of lncRNAs with corresponding proteins, DNA or RNA can be targeted with small molecules. Inhibition of up-regulated lncRNAs with siRNA or ASO presently seems to be the most promising approach as a new treatment modality for the treatment of ESCC. *In vivo* studies in patient-derived xenografts (PDX) of ESCC would increase the translational impact of the approaches described above.

Conflicts of Interest

FB is and UHW was an employee of Roche.

Authors' Contributions

The Authors contributed equally to all aspects of the paper.

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Received March 17, 2022
Revised April 7, 2022
Accepted April 11, 2022