Abstract. The perception of long non-coding RNAs as chunk RNA and transcriptional noise has been steadily replaced by their role as validated targets for a diverse set of physiological processes in the past few years. However, for the vast majority of lncRNAs their precise mode of action and physiological function remain to be uncovered. A large body of evidence has revealed their essential role in all stages of cancirogenesis and metastasis. In this review we focus on the role of lncRNAs in metastasis. We grouped selected lncRNAs into three categories based on in vitro and in vivo mode of action-related studies and clinical relevance for metastasis. Grouped according to their mode of action, in category I we discuss lncRNAs such as CCAT2, DREH, LET, NKILA, treRNA, HOTAIR, H19, FENDRR, lincROR, MALAT, GClncl, BCAR4, SCHLAP1 and lncRNA ATP, all lncRNAs with in vitro and in vivo metastasis-related data and clinical significance. In category II we discuss lncRNAs CCAT1, PCAT1, Ptengp1, GPLINC, MEG3, ZEB2-AS, LCT13, ANRIL, NBAT1 and lncTCF7 all characterized by their mode of action in vitro and clinical significance, but pending or preliminary in vivo data. Finally, under category III, we discuss lncRNAs BANCR, FRLnc1, SPRY4-IT1 and LIMT with partially or poorly-resolved mode of action and varying degree of validation in clinical metastasis. Finally we discuss metastasis-related translational aspects of lncRNAs.

Metastasis is the major cause of death in patients with cancer. It is mediated by a multi-step process referred to as the metastatic cascade (1, 2). Initial steps include local invasion and migration, angiogenesis, epithelial-mesenchymal transition (EMT) and intravasation. Tumor cells enter the circulation as single cells or circulating tumor cell clusters, are coated by platelets to escape an immune response and subsequently arrest in capillaries in distant organs as a prerequisite for extravasation. Colonization starts by homing of tumor cells in supporting niches of the organ parenchyma, followed by a latency phase which can last from several months to decades. A prerequisite for overt outgrowth of micrometastases is their adaptation to the local microenvironment and acquisition of colonization-promoting traits (3-6). The pattern of colonized distant organs depends on the tumor type and can range from predominant spread to one organ and colonization of different types of organs sequentially or simultaneously (7). Several genes and their products have been identified to mediate crucial steps of the metastatic process such as metastasis initiation and progression, as well as organ-specific functions of metastasis (virulence) (8, 9). These gene products include proteases, chemokines, cytokines and their receptors, angiogenic factors, intracellular and transmembrane kinases, adhesion molecules, components of the extracellular matrix (ECM), GPI-linked receptors and carbohydrate metabolism-related enzymes (8, 9). More recently, an important impact of RNA-related molecules for metastasis has emerged. MicroRNAs (miRs) and other types of RNA modulate metastasis via regulatory networks (10, 11). In this review we focus on the role of long non-coding RNAs (lncRNA) as promoters or inhibitors of metastasis in different tumor entities since there is an urgent need to define new targets for therapeutic intervention. With the exception of denosumab for treatment of bone metastases, all other agents evaluated in clinical studies for treatment of metastatic disease gave rise to mixed or disappointing results (6).
Long Non-coding RNA (lncrna) – General Features

Sequencing of the human genome resulted in identification of 20,000 protein-encoding genes which comprise less than 2% of the human genome. However, it was shown that 70% of the human genome is transcribed into RNA yielding many thousands of ncRNAs (12). They can be classified into several subtypes such as housekeeping RNAs, small non-coding RNA (snRNA) and long non-coding RNAs (lncRNAs) (13, 14). Examples for housekeeping RNAs are ribosomal RNA (rRNA), transfer RNAs (tRNAs), small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs). SnRNAs have a length of less than 200 nucleotides (nts), and include microRNAs (miRs), small interfering RNAs (siRNAs), circular RNAs, splice-site RNAs, promoter-associated short RNAs and 3'UTR-derived RNAs as examples. LncRNAs are arbitrarily defined by their size exceeding 200 nts and apparent lack of protein-coding capacity. 14,880 human lncRNAs have been identified in the context of the ENCORE project (15). LncRNAs are products of polymerase II (pol II), which are nearly always capped, polyadenylated and frequently spliced (16). They can be categorized into sense, antisense, bidirectional, intronic and intergenic lncRNAs (17). The identification of lncRNAs was accelerated by high-throughput RNA sequencing (RNA-Seq) and its combination with bioinformatic algorithms (18). Transcriptional profiling studies have underlined prevalence and function of lncRNAs in human cancer (19). Five thousand and thirty-seven tumor specimens across 13 cancer types from The Cancer Genome Atlas (TCGA) and 935 cell lines from the Cancer Cell Line Encyclopedia were sequenced. Significant deregulation in lncRNA expression was noted in comparison to corresponding normal tissues was noted indicating tumor and lineage specific alterations, copy number changes, epigenetic modifications such as promoter methylation and cancer-associated single-nucleotide polymorphisms (SNPs).

LncRNAs exert their functions through interactions with other components such as proteins, RNAs and DNAs (20). RNA-protein, RNA-RNA and RNA-DNA interactions can be combined by a single lncRNA to build distinct functionality conferring complexes (20). As archetypic functions of lncRNAs, guide-, decoy- and scaffold functions have been identified (21). The guide function mediates recruitment of chromatin-modifying enzymes to target genes in cis- or trans, chromatin remodeling and epigenetic regulation of target genes (22). The decoy function involves binding of miRs through lncRNAs (miR sponges), titration of transcription factors away from chromatin or recruitment of protein factors into nuclear subdomains (16). The scaffold function of lncRNAs can mediate stabilization of ribonucleoprotein complexes such as signaling modules and nuclear structures often accompanied by allosteric modification of protein activity (14).

Many of the functions of lncRNAs are transcription-related, such as forming chromatin-modifying complexes, acting as transcriptional co-activators, mediating chromatin-looping by enhancer-derived lncRNAs or the functioning as natural antisense transcripts (NATs) (23, 24). Modulation of transcription of oncogenes or tumor-suppressor genes is an oncology-related function of lncRNAs (25). Post-transcriptional functions of lncRNAs can trigger alternative splicing by pairing with other RNAs (16, 26).

LncRNAs often associate with the polycomb repressive complexes (PRC1 and PRC2) and histone methyltransferase G9a to introduce post-translational modifications to specific amino acids in histone tails, resulting in negative regulation of RNA pol II. PRC1 is a multiprotein complex composed of proteins such as BMI1, RING1, RING2 and chromobox proteins (CBX) and is able to ubiquitinylate histone H2A at lysine 119 (26, 27). PRC2 is assembled by EED, SUZ12 and histone methyltransferase EZH2 which trimethylates histone 3 lysine 27 (26, 27). G9a introduces a repressive mark by trimethylation of histone 3 lysine 9 (28). In addition to mediating covalent modifications of histones, lncRNAs can be involved in modulation of nucleosome positioning to regulate expression of genes. An example is the SWI/SNF complex which mediates restructuring of chromatin based on hydrolysis of ATP (29).

The physiological function of lncRNAs was demonstrated by multiple knock-out models which indicated their requirement for life and brain development (30). Eighteen lncRNA knock-out strains were generated, focussing on intergenic lncRNAs whose deletion would not overlap known protein coding genes or other gene annotations. Perinatal and postnatal phenotypes were observed in three mutant strains and growth defects in two additional strains. Knockdown of FENDRR, an lncRNA discussed later in this review, resulted in defects of the lung, gastrointestinal tract and heart in neonates (19) defining it as a functional moiety.

Metastasis-related lncRNAs – Category I

In this category we summarize metastasis-related lncRNA with data supporting mode of action (MOA), in vivo metastasis-related data and clinical data with respect to their role in metastasis. They are grouped according to their MOA. We discuss lncRNAs which function through RNA/protein interaction such as CCAT2, DREH, LET, NKILA and treRNA, or through epigenetic modification alone or in combination with other mechanisms such as HOTAIR, H19, FENDDR, lincROR, MALAT, GCln1, BCAR4, SCHLAP1 and finally we discuss lncRNA ATP which functions by induction of miRs and mRNA stabilization.

Colon-cancer Associated Transcript 2 (CCAT2). CCAT2 was discovered in microsatellite-stable colorectal cancer (CRC)
as a highly overexpressed lncRNA (31). CCAT2 is up-regulated in breast cancer and correlates with poor prognosis for a specific subgroup of patients (32, 33). CCAT2 is localized mainly in the nucleus and its MOA is based on RNA-protein interaction as outlined in the following. A high-risk allele for CRC, SNP rs6983267 has been shown to produce more CCAT2 transcript than its corresponding allele (31, 34). In vitro inhibition of CCAT2 decreases cell proliferation and invasion of both MCF7 and MBA-MB 231 breast cancer cells (32). In HCT116 colorectal cancer cells, transduced CCAT2 increases migration and in the highly metastatic colon cancer variant KM12SM, knock-down of CCAT2 reduces invasion (31). Mechanistic resolution points to activation of Wnt signaling by CCAT2 by physical interaction with transcription factor TCF7L2 (TCF4) (31). However, the mechanistic details of these findings have to be resolved. Wnt signaling leads to up-regulation of target genes such as c-MYC and CD44 as well as metastasis-promoting miR17-5p and miR20a. The involvement of Wnt signaling in metastasis is well documented (35, 36) and aberrant Wnt-signaling in CRC has been observed previously (37). Interestingly, CCAT2 is also up-regulated by Wnt signaling, pointing to a feedback loop. Involvement of CCAT2 in metastasis has been shown with HCT116 cells. Injection of HCT116 cells overexpressing CCAT2 into the spleen of nude mice gave rise to higher incidence of liver metastasis and greater numbers of metastatic nodules (31).

LncRNA DREH (Down-regulated expression by HBx), DREH was discovered in a transgenic mouse model of hepatocellular carcinoma (HCC) induced by expression of Hepatitis B virus X protein (HBx) in the liver (39, 39). DREH is down-regulated in murine tumor tissue compared to normal liver tissue as shown by comparison of the profile of lncRNAs in both types of tissues (38). The human ortholog of DREH is also down-regulated in human HBV-related HCC tissue and DREH expression levels correlate with relapse-free and overall survival (38). As outlined in the following, the MOA of DREH relies on RNA-protein interaction. The tumor-suppressive function of DREH is mediated by change of the structure of the cytoskeleton due to binding to vimentin and repression of vimentin expression (38). Vimentin is an intermediate filament protein which is known as a marker of mesenchymal cells and of cells undergoing epithelial mesenchymal transition (EMT) during metastatic progression (40-42). In addition to maintainence of cell morphology, vimentin is also involved in cell adhesion, migration, proliferation and signal transduction (43). Down-regulation of DREH in HCC cells by RNA interference promotes migration and invasion (38). DREH also has an impact on proliferation and metastasis in vivo. Hepa-1-6 cells transfected with DREH exhibited decreased tumor growth in nude mice (38). Tail vein injection of these cells gave rise to less pulmonary metastases in comparison to control cells (38). In an orthotopic liver cancer model in nude mice, Hepa-1-6 cells transfected with DREH gave rise to reduced intrahepatic nodules as well as reduced metastasis in the abdominal cavity and wall, intestine and lymph nodes (38).

LncRNA LET (Low expression in tumor). LncRNA LET is down-regulated in hepatocellular carcinoma (HCC) and correlates with metastasis (44, 45). Its MOA relies on binding to NF90 in a 1:1 stoichiometry resulting in ubiquitinylation and degradation of NF90 (2). NF90 is a double-stranded RNA binding protein implicated in stabilization, transport and translational control of target mRNAs including HIF-1α, ced42 and dual specificity protein phosphatase DUSP (46) as well as mediating the degradation of these targets. HIF-1α (47, 48), ced42 (49) and DUSP (50) are validated mediators of metastasis. Down-regulation of lncRNA LET in HCC cell lines and patient’s tumors is mediated by histone deacetylase 3 (HDAC3) (45). Transwell experiments have indicated that hypoxia increases the invasive potential of HCC SMCC-7721 cells and up-regulation of lncRNA LET diminishes invasion in vitro and under hypoxic conditions (45). In vivo experiments with HCC cell lines SMCC-7721 and HCCLM3 as well as colon carcinoma SW480 cells with ectopic expression of lncRNA LET indicated that lncRNA LET inhibits lung colonization after tail vein injection (45). In an orthotopic liver xenograft model, lncRNA LET overexpression reduced hepatic invasion and abdominal metastasis (45). Furthermore, short hairpin ribonucleic acid (shRNA) directed against lncRNA LET increased lung metastasis after tail vein injection (45). In addition, orthotopic injection of HCC cell line Huh7 (45).

NKILA (NFkB-activating lncRNA). As outlined in the following, NKILA is an inhibitor of metastasis in pre-clinical models in vitro and in vivo and its MOA relies on protein-RNA interaction. NKILA was found to be expressed at lower levels in breast carcinomas without distant or regional lymph node metastasis and further reduced in those with metastasis, predicting poor clinical outcome (51). NKILA was identified as a lncRNA induced by NF-κB-signaling activating inflammatory cytokines such as TNFα and IL-1β in MDA-MB 231 breast cancer cells by microchip-based technology (51-53). NF-κB is a mediator of invasiveness and NKILA acts as a negative regulator of NFkB signaling (51, 53). It stably associates with the NFkB-IκB complex and binds to two different sites of the homodimeric p65 subunit of NFkB (54). Thus, IκB kinase (IKK)-related phosphorylation sites on inhibitor of κB (IkB) are masked and therefore NFkB-signaling is inhibited due to interaction of NKILA with functional domains on signaling proteins (Figure 1A). It should be noted that abnormal NFkB activation and poor patient outcome are based on degradation of NKILA by miRs.
enhancer-like function on expression of transcription factor snail in cis, however, the mechanism by which gene expression is enhanced is not yet resolved (56). Subsequently ncRNAa7 was renamed to treRNA because it regulates metastasis at the translational step based on RNA-protein interaction (57). treRNA was identified as an lncRNA overexpressed in breast cancer lymph node metastasis compared to matching primary breast tumors (57). Functional studies have delineated a metastasis-promoting function of treRNA in vitro and in vivo. Knock-down of treRNA in A549 lung cancer cells suppressed cell migration and invasion, but did not affect proliferation (57). Enforced expression of treRNA in non-invasive MCF-7 cells increased cell migration and invasion through Matrigel (57). Tail vein injection experiments of A549 cells and A549 siRNA treRNA expressing cells indicated abolishment of lung metastasis in mice injected with A549 siRNA treRNA cells (57). MCF-7 cells ectopically expressing treRNA gave rise to lung metastasis after implantation into the mammary fat pads, whereas MCF-7 cells did not colonize the lungs. A key mechanism for promotion of metastasis is based on treRNA-mediated suppression of translation of epithelial markers such as E-cadherin (57). treRNA is assembling a translation-modulating ribonucleoprotein complex involving several RNA binding and additional proteins (57). Knock-out experiments in MCF-7 cells expressing treRNA revealed that hnRNPK and FXR2 are required for the treRNA function on metastasis in vivo (58-60). Ribonucleoprotein complex RNPK (3, 4) is involved in multiple steps of gene expression, including translation and FKR2 (60) can associate with ribosomes to form RNP complexes. In addition, translation initiation factor eIF-4G1 (61) was found to associate with the tre-RNA based ribonucleoprotein complex. The complex exerts its translation modulatory function by interaction with the 3′UTR of its target genes such as E-cadherin (Figure 1B). The precise mechanism of translation inhibition, however, remains to be resolved.

**HOX Antisense Intergenic RNA (HOTAIR).** Expression of HOTAIR correlates with metastasis and poor prognosis in breast, colon and lung cancer (62-64). HOTAIR is derived from HOX C, but functions in trans at the HOX D locus (65). HOTAIR recruits the PRC2 complex and the dimethylase LSD1, promoting an increase in the repression code H3K27me3 and a decrease in the activation code H3K4me3. Forcing expression of HOTAIR in non-transformed breast and lung cancer cell lines has been shown to promote growth in...
soft agar and invasion in matrigel (70). Another aspect of the MOA of HOTAIR was revealed by its binding to miR-331-3p, resulting in increased expression of HER2, promoting metastasis (71, 72). There is also evidence that HOTAIR can interfere with DNA methylation, because depletion of HOTAIR in HepG2 HCC cells has been correlated with a decrease in phosphatase and tensin homolog (PTEN) promoter methylation (73). In vivo, the impact of HOTAIR on metastasis was demonstrated with human breast cancer cells after tail vein injection. Expression of HOTAIR in MDA-MB231 cells gave rise to an 8-10 fold increase of nodules in the lungs (70). Altogether, these results substantiate that HOTAIR-mediated reprogramming of the chromatin state can promote metastasis. TCGA-based transcript analysis confirms overexpression of HOTAIR in breast-, colon- and lung tumors and in addition HOTAIR is up-regulated in stomach cancer in comparison to matching normal tissues (Figure 2C).

**LncRNA H19.** LncRNA H19 is an oncofetal antigen that is only marginally expressed in normal human tissues (74). It is up-regulated in several types of tumors such as colorectal cancer (CRC), HCC, breast- and bladder cancer and may be involved in metastasis of these types of tumors (75). Taken together, there is evidence that the functions of H19 are context specific, dependent on stage and type of tumors (75). In the following we focus on findings supporting the prometastatic function of H19. One has to keep in mind that processing of H19 gives rise to miR675, a 23 nt miR located at its 3' end and the residual sequences of H19, which leaves the functional contribution of both moieties difficult to differentiate in most of the reported experiments (75). Evidence for involvement of H19 in metastasis includes H19-mediated induction of genes mediating invasion, promotion of EMT and Wnt signaling. In T24 bladder carcinoma cells, H19 induces angiogenesis and metastasis promoting genes (74). In CRC cells, H19 activates EMT-related markers such as vimentin, ZEB1 and ZEB2, promoting cell migration by functioning as a sponge for miR-138 and miR-200a (76). Another invasion promoting ability of H19 is the activation of constitutive Wnt signaling (77). In bladder cancer T24 cells, H19 was shown to recruit histone lysine N-methyltransferase enhancer of Zeste homolog 2 (EZH2) resulting in activation of Wnt/β-catenin signaling by inhibition of expression of Nkd1, an antagonist of Wnt signaling, through methylation of its promoter (77). In gastric cancer cells MKN45 and SGC7901, H19 was shown to be involved in proliferation, migration, invasion and metastasis (78). This was demonstrated through H19 knock-down in MKN45 cells and ectopic expression of H19 in SGC7-901 cells and their assessment in transwell and woundhealing assays (78). In this context, ISM1 was identified as a binding protein for H19 and CALN1 as a target gene for miR-675 (78). SGC7-901/H19 cells, subcutaneously injected into nude mice showed increased tumor growth and increased number of peritoneal nodules after injection into the peritoneal cavity (78). Reciprocal in vivo observations were made with MKN45 H19 knock-down cells (78). Assessment of these cell lines in additional metastasis-related models would be helpful for evaluation of the in vivo function of H19 in metastasis. TCGA-based transcript analysis indicates increased steady-state levels of H19 RNA in CRC and stomach cancer, but not in breast cancer as outlined above (Figure 2A).

**FENDRR.** FENDRR (79) is an lncRNA with decreased expression in gastric cancer correlating with poor prognosis (80). FENDRR mediates dsDNA-RNA triplex formation to epigenetically regulate expression of target genes by recruitment of PRC2 (80, 81). Overexpression of FENDRR in gastric cancer cells suppresses migration in vitro by down-regulating fibronectin 1 (FN1) and MMP2/MMP9 expression (80). Down-regulation of FENDRR in gastric cancer cells was found to be due to histone acetylation by HDAC3. As previously outlined, FENDRR is essential for proper heart and body wall formation in the mouse (81). In vivo demonstration of FENDRR involvement in metastasis was performed by tail vein injection of MGC 803 gastric cancer cells stably transfected with a FENDRR expression vector. Ectopic expression of FENDRR significantly reduced the number of nodules in the lung compared to those in the control group (80).

**Linc-ROR.** Linc-ROR was originally identified as a lncRNA overexpressed in breast cancer tissues and TNBC versus corresponding normal tissues as well as in a panel of breast cancer cells in comparison to immortalized breast epithelial cells (82, 83). Clinical studies correlating linc-ROR expression with survival and metastasis are still pending. Several
preclinical studies are supportive regarding a possible role of linc-ROR in metastasis. For example, linc-ROR was shown to promote invasion and migration of breast cancer cells (82). Furthermore, linc-ROR can act as a promoter of EMT by functioning as a sponge for miR-205 and preventing degradation miR-205 target genes including EMT-inducer ZEB2 (82). An additional decoy-related functional contribution of linc-ROR was revealed in gastrointestinal cancer cells (84). Linc-ROR was shown to repel G9A methyltransferase promoting release of H3K9 methylation by binding to and activation of the tescalin promoter that mediates expression of tescalin, an EF-handed calcium-binding protein (85). In TNBC, linc-ROR was shown to be overexpressed and to act as a competitive RNA for miR-145, resulting in up-regulation of ADP-ribosylation factor 6 (ARF6), a small GTPase known as a regulator of breast cancer (83, 86). In vivo experiments suggest a role of linc-ROR in metastasis, since tail vein injection of shROR expressing MDA-MB-231 cells exhibited fewer and smaller lung metastatic foci than controls (82). However, it is unclear if the effect was due to less metastatic or overall lower tumorigenic properties of these cells as the growth of primary tumors was also slower. Therefore, further experiments are needed to resolve the mode of action of linc-ROR in metastasis.

Metastasis-Associated Lung Adenocarcinoma Transcript (MALAT1). MALAT1 is also referred to as Nuclear Enriched Abundant Transcript 2 (NEAT2). MALAT1 expression is prognostic for survival of patients with stage I lung adenocarcinoma or squamous cell carcinoma and in bladder carcinoma its expression levels correlate with metastasis (87, 88). Furthermore MALAT1 is expressed in several types of cancer (89). The incidence of lymph-node metastasis in patients with high MALAT1 expression is higher than in patients with low MALAT1 expression across several types of tumors as shown in a meta-analysis of cancer patients in China (90). The involvement of MALAT1 in alternative splicing is still a controversial issue. This possible engagement was supported by the colocalization of MALAT1 to nuclear speckles, structures enriched in polyA mRNA and factors involved in mRNA processing, splicing and export in HeLa cells, antisense oligonucleotide (ASO)-based depletion of MALAT1 has supported its involvement in alternative splicing by modulating serine/arginine (SR) splicing factor phosphorylation (91). However, in a panel of lung cancer cells, down-modulation of MALAT1 mRNA by introducing destabilizing elements using Zn-finger nucleases into its mRNA did not give rise to changes in the splicing pattern (92). The latter finding is compatible with MALAT1 knock-out mice which are viable and fertile and do not show any phenotype or splicing alterations, despite the strong evolutionary conservation of MALAT1 (93, 94). However, involvement of MALAT1 in regulation of transcription is consistently supported by several investigations. An example is control of cell-cycle-related genes by their recruitment from transcriptionally inactive polycomb bodies (PcG) to transcriptionally active interchromatin granules (ICG) (95). This phenomenon is triggered by the methylation status of polycomb2 (Pc2), also referred to as CBX4, a member of the PRC1 complex (95). Methylated Pc2 localizes ncRNA TUG1 to the PcGs, whereas unmethylated Pc2 sequencers MALAT-1 into ICGs. Pc2 acts as a reader of the histone code through its chromodomain by binding to H2AK5ac and H2AK13ac, which are markers of gene activation and subsequent pol II activation (Figure 1D). Further evidence for involvement of MALAT1 in transcriptional regulation has been obtained in pancreatic cancer and bladder carcinoma cells. Ectopic expression of MALAT1 in pancreatic cancer cells is associated with loss of E-cadherin and gain of function such as N-cadherin, vimentin and TGFβ (96). MALAT1 knock-down in T24 bladder carcinoma cells leads to down-regulation of EMT promoting factors such as Slug, Zeb1 and Zeb2 as well as decreased nuclear localization of β-catenin (88). Metastasis-related experiments were performed with lung cancer cell lines A549 and EBC-1 in which MALAT1 is a driver of mobility (92). MALAT1 is required for effective lung nodule formation of A549 cells after tail vein injection. 80-90% reduction of the number of lung nodules was observed for A549 MALAT1 knock-out cells. In a model covering all steps of the metastatic cascade, EBC-1 cells were subcutaneously injected, the tumors were excised after five weeks of treatment with MALAT1 ASO and the lung metastases were assessed after 7 weeks without further ASO treatment. Fewer and smaller nodules were observed in the ASO group. It should be noted that MALAT1 does not effect cell proliferation of EBC-1 cells in vitro and only exerted a minor impact on growth of the primary tumor in vivo. TCGA-based transcript analysis does not support up-regulation of MALAT-1 in bladder und lung carcinoma as outlined above, however, increased expression in prostate and liver cancer in comparison to normal tissues was noticed (Figure 2B).

GClncl. GClncl was identified by comparison of lncRNA expression profiling in gastric cancer and adjacent normal tissue and its up-regulation correlates with poor prognosis in patients with gastric cancer (97). In gastric cancer cell lines BGC 823, MKN 45 and GES-1, GClncl mediates proliferation and invasion as shown by a combination of ectopic expression and small interfering RNA (siRNA) experiments (97). Metastasis-promoting capability of GClncl was assessed in nude mice with GES-1 and MGC 803 cells after subcutaneous implantation and injection of adenovirus expressing GClncl or sh GClncl. The experiments revealed a positive impact of GClncl on metastasis of these cell lines to the lungs (97). MOA studies revealed that GClncl acts as a scaffold for WDR5 (98) and KAT2A (99). WDR5 is a core subunit of the
H3K4 methyltransferase complex and KAT2A functions as a histone acetyl transferase via H3K9 acetylation in the promoter region. One of the genes affected by GClncl is mitochondrial superoxide dismutase (SOD2). Binding of WDR5 and KAT2A to its promoter results in its transactivation due to increased H3K4 trimethylation and H3K9 acetylation (97) (Figure 1E). SOD2 has been shown to be elevated in gastric cancer and regulation of metastasis (100, 101).

LncRNA BCAR4 (Breast Cancer Anti-estrogen Resistance). LncRNA BCAR4 was originally identified by its ability to confer resistance against anti-estrogens in breast cancer cells (102, 103). BCAR4 also functions as a breast cancer oncogene (104) and its expression correlates with advanced breast cancer (105). The Oncomine database also showed a significant correlation between BRCA4 expression and metastatic colorectal, rectal, lung- and prostate cancer (105). Recently, a metastasis-promoting function of BCAR4 for breast cancer cells was uncovered based on cooperative regulation of downstream chemokine signals (105) as outlined in the following. Interaction between chemokine CCL21 and its receptor CCR7 (106) activates rho-interacting serine/threonine kinase 21, citron (CIT) (107), which phosphorylates transcription factor GLI-2 (108), which is subsequently translocated into the nucleus. BCAR4 is required for the transcriptional activation of phospho-GLI2-dependent target genes in breast cancer cells. In response to CCL21, BCAR4 binds to Smad Nuclear Interacting Protein 1 (SNIP1) (109) and serine/threonine phosphatase regulatory subunit 10 (PSP1R10) also known as PNUTS (110). Interaction of phospho-GLI2 with SNIP1 releases SNIP1-mediated inhibition of p300-dependent histone acetylation, which results in binding of PNUTS to H3K18ac, thereby releasing inhibition of pol II via activation of phosphatase PP1 (Figure 1F) (111). In vitro, BCAR4 acts as a promoter of invasion and migration of breast cancer cells (105). In vivo BCAR4 functions as a mediator of breast cancer metastasis in preclinical models. Lung metastasis of MDA-MB 231 LM2 cells harboring shRNA directed against BCAR4 was significantly reduced after their injection into mammary fat pads in comparison to control cells (105). Locked nucleic acids (LNAs) targeting BCAR4 reduced lung metastasis of MDA-MB 231 LM2 cells after i.v. administration twice a week for three weeks, underlining the importance of BCAR4 as a therapeutic target (105). TCGA-based transcript analysis confirms overexpression of BCAR4 in colon-, lung- and prostate cancer and in addition indicates overexpression in bladder-, breast- and stomach cancer in comparison to normal matching tissues (Figure 2D).

SCHLAP1 (Second Chromosome Locus Associated with Prostate-1). SCHLAP1 is expressed in 25% of prostate cancers and is a predictor of poor outcome, metastasis and mortality (112, 113). SCHLAP1 interacts with chromatin complex SWI/SNF and binds to and disrupts function of SNF5, a core component of this complex (114). SCHLAP1 antagonizes the genome-wide localization, regulatory and tumor-suppressive functions of the SWI/SNF complex (115, 116) due to its impaired ability to regulate gene expression properly. SCHLAP1 overexpressed in benign immortalized prostate cells increases invasion with no impact on proliferation (114). Likewise, knock-down of SCHLAP1 in 22Rv1 prostate cancer cells impairs cell invasion in vitro (115). Intra-cardiac injection of SCHLAP1 knock-down 22Rv1 cells abolished metastatic seeding at proximal (lungs) and distant sites (115). Altogether, these data support involvement of SCHLAP1 in metastasis of prostate cancer.

LncRNA-ATB (lncRNA activated by TGFβ). LncRNA-ATB is up-regulated by TGFβ and its high expression is a robust predictor of survival in patients with HCC (117). Its MOA is based on two different types of RNA-RNA interactions as outlined in the following. TGFβ is able to induce metastasis-suppressing as well as metastasis-promoting genes (118-120). LncRNA-ATB can mimic the pro-metastatic role of TGFβ by inducing miRs of the miR-200 family (121, 122) and by promoting IL11 signaling (Figure 1G) (123). LncRNA-ATB up-regulates EMT- and invasion-promoting transcription factors ZEB1 and ZEB2 by competitively binding to miR200 family members, thus promoting an early step of the metastatic cascade (121, 122). Additionally, lncRNA-ATB binds to IL11 mRNA resulting in its stabilization and increased expression and secretion, thus promoting IL11/STAT3 signaling which is essential for colonization of distant organs (Figure 1G) (123). In vitro, lncRNA-ATB induces EMT and invasion after its overexpression in SMMC-7721 HCC cells (117). The previous findings are also reflected in preclinical in vivo models. Ectopic expression of lncRNA-ATB in HCC cells increased the number of CTCs and vice versa, its depletion resulted in decreased numbers of CTCs (117). In an orthotopic model with HCCLM6 cells, depletion of lncRNA-ATB resulted in inhibition of intrahepatic, mesenteric and pulmonary metastases (117). In a tail vein-injection metastasis experiment with SMMC-7721 cells overexpressing lncRNA-ATB, an increase in lung metastasis in comparison to control cells was noted (117).

Metastasis-related lncRNAs: Category II

In this category we summarize lncRNAs with MOA-supporting experiments and correlation with metastatic disease, but with pending experiments supporting metastasis-promoting role in preclinical in vivo models. We discuss CCAT1 and PCAT1 with a sponge-based mechanism, PTEPpg1, GAPLINC and MEG3 with sponge function and additional MOA, ZEB2-AS, LCT13 and ANRIL with an
antisense-based MOA as well as NBAT1 and IncTCF7 with a MOA due to epigenetic modifications.

*Sponge-based mechanism.* Colon cancer associated transcript 1 (CCAT1) is up-regulated in CRC, gastric cancer and HCC and correlates with bad prognosis in HCC (124-126). In CRC cells, CCAT1 mediates cell proliferation and enhanced transcription of c-MYC by regulating long-range chromatin interactions at the c-MYC locus (127). Prostate cancer associated transcript-1 (PCAT-1) was identified as a mediator of proliferation based on interaction with miR-3667-3p resulting in stabilization of c-MYC (128). However, a role of PCAT-1 in proliferation and migration has been described in NSCLC (129) and HCC (130).

*Sponge-based and additional MOA.* PTENgp1 is an lncRNA involved in modulating PI3K-AKT signaling, a pathway crucial for proliferation and metastasis, frequently activated by inactivation of tumor suppressor PTEN which results in PI3K phosphorylation and subsequent activation of AKT (131-133). PTENgp1 is encoded by PTENP1, a pseudogene of PTEN, exhibits tumor- and metastasis-suppressive activity via its 3'-UTR by acting as a sponge for PTEN degrading miR17 and miR21 (134). A further complexity of this type of gene regulation is exerted by an antisense RNA to PTENgp1 that is expressed in two isoforms α and β (134). Isoform α functions in trans and localizes to the PTEN promoter and epigenetically modulates PTEN transcription by DNA methyltransferase 3a (DNMT3a) and EZH2 (134). Isoform β interacts with PTENgp1 through RNA-RNA pairing, facilitates PTENgp1 export to the cytoplasm and modulates its stability and sponge activity (134). Function of gastric adenocarcinoma predictive large intergenic non-coding RNA (GAPLINC) is based on a sponge-related and RNA-protein related MOA (135, 136). GAPLINC is associated with shorter survival in a subset of patients with gastric cancer, which overexpress this lncRNA (135). GAPLINC mediates cell migration through regulation of CD44 acting as a sponge for miR 211-3p in gastric cancer cells (135). In CRC cells, GAPLINC promotes cell proliferation and invasion in vitro by binding to PTB-associated splicing factor (PSF) and non-POU-domain-containing octamer binding protein (NONO), factors which are involved in up-regulation of EMT-promoting factor SNAI-2 (136). For maternally expressed gene 3 (MEG3) lncRNA, sponge-related and RNA-DNA triplex formation based MOA has been described (137, 138). MEG3 is decreased in gastric cancer patients and cell lines and down-regulation correlates with metastatic disease. Ectopic expression of MEG3 inhibits cell proliferation and migration and promotes apoptosis in several gastric cancer cell lines probably due to sequestration of oncosgenic miR-181 (137). Another functional aspect of MEG3 was revealed in several types of cancer cell lines as its capacity to negatively regulate EMT-promoting TGFβ pathway genes (138). This function is based on guiding MEG3 to chromatin through RNA-DNA triplex formation at distal regulatory elements of these genes via GA-rich sequences and subsequent recruitment of PRC2 (138). TCGA-based transcript analysis could not confirm down-regulation of MEG3 in gastric cancer, however, we have noted down-regulation of MEG3 in bladder-, breast- and liver cancer in comparison to matching normal tissues (Figure 2E).

*Antisense-based MOA.* ZEB2-AS1, LCT13 and ANRIL are lncRNA with an antisense-based mechanism. ZEB2-AS1 is a natural antisense transcript that enables translation of ZEB2, an EMT-inducing transcription factor, which represses genes encoding functional proteins such as E-cadherin (139, 140). Splicing of an intron in the 5'UTR of ZEB2 prevents translation of ZEB2 mRNA and ZEB2-AS1 abolishes splicing and enables translation of ZEB2 mRNA due to an internal ribosome binding site located in the intron (139, 141). Possible clinical relevance of ZEB2-AS1 was demonstrated in urinary bladder cancer (UBC) (142). TGFβ1 secreted by fibroblasts was shown to induce ZEB2 expression, migration and EMT of bladder cancer cells dependent on ZEB2-AS1 (142). TGFβ1 expression and ZEB2-AS1 transcript levels were positively correlated in bladder carcinoma specimens, pointing to a role of the TGFβ1-ZEB2-AS1-ZEB2 axis in metastasis of this type of cancer (142). Another IncRNA in this category, LINE-1 chimeric transcript 13 (LCT13), inhibits expression of human tissue factor pathway inhibitor (TFPI-2) (143). It acts as a matrix-associated Kunitz inhibitor and its anti-metastatic effect is due to inhibiting the activation of zymogen matrix metalloproteinases involved in tumor progression, invasion and metastasis (144, 145). LCT13 induces silencing and deposition of repressive histone modifications in breast cancer and colon cancer cells (143). Clinical relevance of LCT13 is suggested by the finding that in 56% (n=27) of colorectal tumors with reduced TFPI-2 expression, LCT13 transcripts were detected (143). Antisense non-coding RNA in the INK4 locus (ANRIL) is an lnc RNA whose expression level predicts poor prognosis in patients with HCC, NSCLC and ovarian cancer (146-148). ANRIL functions as a cis-regulator of the INK4a/ARF/INK4b locus of tumor suppressors by acting as an antisense RNA and by its capability to recruit PRC1 and PRC2 complexes, which mediate epigenetic regulation of this locus (149, 150). In vitro experiments with HCC, NSCLC and ovarian cancer cell lines indicate that ANRIL is able to promote proliferation, migration and invasion (146-148, 151). In thyroid carcinoma cells, these effects are based on repression of TGFβ1/Smad signaling and up-regulation of p15/INK4b. ANRIL silencing inhibited experimental metastasis of TPC-1 thyroid cancer cells.
carcinoma cells and TGFβ1 siRNA was able to reverse the decline of visceral metastases seen by silencing ANRIL (151). Since the details of the MOA of ANRIL in thyroid carcinoma cells have not been worked-out yet and in vivo data have only been reported for thyroid carcinoma cells we have maintained ANRIL as a class II metastasis-related lncRNA.

**MOA based on epigenetic modification.** Neuroblastoma associated transcript-1 (NBAT-1) lncRNA and lncRNA T-cell factor 7 (lnc TCF-7) function by epigenetic modification of target genes. NBAT-1 exhibits a tumor-suppressive function in neuroblastoma and breast cancer and low expression of NBAT-1 correlates with poor survival in these types of tumors (152, 153). Loss of NBAT-1 increases proliferation and migration of neuroblastoma cells due to expression of a set of genes which are repressed by NBAT-1 due to recruitment of EZH2, the catalytic component of PRC2 (152, 153). NBAT-1 is critical for neuronal differentiation of neuroblastoma cells through its downstream effectors SOX9 and neuronal-specific transcription factor NRSF/REST. In addition, NBAT-1 inhibits invasion and proliferation of breast cancer cells due to activation of Wnt signaling through inactivation of dickkopf Wnt signaling inhibitor 1 (DKK1) via recruitment of PRC2 (153). The last lncRNA to be discussed is lncTCF-7, which has been studied in HCC and shown to be involved in renewal of human liver cancer stem cells (CSCs) and HCC aggressiveness through promotion of EMT (154, 155). Self-renewal of liver CSCs is mediated through recruitment of the SWI/SNF chromatin remodeling complex resulting in activation of Wnt signaling through lncTCF-7 (154). Activation of EMT in HCC cells is initiated by inflammatory cytokine IL6 which activates lncTCF7 expression through binding of STAT3 to the lncTCF7 promoter (155). RNA interference based attenuation of lncTCF7 prevented IL6-induced EMT and invasion of SK-Hep1 HCC cells (155).

**Metastasis-related lncRNAs: Category III**

In this category we describe a melanoma, two gastric cancer-related and a breast-cancer related lncRNA with metastasis-modulating potential, which have only partially or poorly resolved MOA and varying degree of validation with respect to involvement in clinical metastasis. BANCR (BRAF-regulated lncRNA) was identified by RNA seq comparison of BRAF V600E transduced and control human melanocytes, and for insights in clinical revalance, BRAF-mutated human melanomas (156). Knock-down of BANCR reduces melanoma migration without affecting viability and proliferation. BANCR regulates a panel of genes involved in cell migration. In the less motile BANCR silenced melanoma cells, CXCL11 expression was down-regulated and impaired invasion could be rescued by exogeneous addition of CXCL11 (156). FRLnc1 (FOXM1-related lncRNA) was found to be induced by transcription factor FOXM1 in gastric cancer cells (157) and its steady-state mRNA levels are increased in 50% of gastric cancers. FRLnc1 increases expression of the EMT-mediators TGFβ1 and Twist and promotes migration of gastric cancer SGC 7901 cells ectopically transfected with FRLnc1, as shown by transwell and wound-healing assays (157). Tail vein injection experiments of these cells reveal promotion of lung metastases in comparison to control SGC 7901 cells (157). SPRY4-IT1 (SPRY4 intronic transcript 1) is derived from an intron of the SPRY gene and its decreased expression in gastric cancer correlates with overall survival (OS) and disease-free survival (DFS) (158, 159). Its down-regulation in cancer tissue seems to be based on promoter methylation. Target validation experiments in SGC 7901, BGC 823 and MKN 45 gastric cancer cells point to its role in inhibition of proliferation, colony formation, cell migration and invasion and its capacity to up-regulate cyclin D1, MMP2, MMP9 and E-cadherin and to down-regulate vimentin (158, 159). Ectopic expression of SPRY4-IT in BGC 823 cells reduced the number of metastatic nodules after tail vein injection (158).

As a prototype of a metastasis-suppressing lncRNA, lncRNA limiting metastasis (LIMIT) was recently discovered (160). LIMIT is down-regulated in aggressive basal-like breast cancer and is suppressed by EGF. The abundance of LIMIT predicts clinical outcome of breast cancer patients (160). LIMIT acts as an inhibitor of motility in vitro and inhibits lung metastasis after tail vein injection of MDA-MB-231 breast cancer cells (160). However, its MOA needs to be worked out in more detail.

**Therapeutic Aspects**

As outlined in the preceding chapters, metastasis-related lncRNAs can be either up- or down-regulated. Selection for therapeutic targets will be based on data including identification of tumor types with deregulated expression, abundance of expression and cellular localization. In addition, MOA studies such as identification of interacting partners such as DNA, RNA or protein, in vitro and in vivo metastasis-related assays and efficacy studies as well as correlation of expression with metastatic risk and survival in patients will all be important for target identification (161-165). In case of down-regulated metastasis-suppressing lncRNAs, substitution therapy with liposomes or nanoparticles delivering plasmid-based expression vectors or expression of the corresponding lncRNA with viral vectors are options for interference. However, optimisation of delivery is a pending issue. In case of overexpressed metastasis-promoting lncRNAs, silencing and MOA-dependent interference are possible options for therapeutic intervention. Tools for silencing are ASOs, liposome-delivered RNAi and vector-expressed shRNAs.
ASO might be most suitable when the target functions in the nucleus, whereas duplex RNA may be the best choice when the target is located in the cytoplasm (166). These tools are the first option for inhibition of lncRNA/RNA or DNA interactions such as inhibition of lncRNA-DNA-DNA triple helix formation at genomic loci (167) or inhibition of natural antisense transcripts (168). An additional mode of intervention is to block the interaction of IncRNA with proteins mediated by domain-domain interactions involved in epi-genetic or translational control. Decay RNAs derived by systemic evolution of ligands by experimental enrichment (SELEX) (169, 170) or small molecules competing for domain-domain interaction by mimicry of the secondary structure of binding partners are candidates for disrupting domain-domain interactions (165, 171, 172). Another option is inactivation of IncRNA structure due to blocking of correct folding (171). Proof-of-concept for inhibition of this type of interaction is the identification of aminoglycoside-based antibiotics that interact with ribosomal RNA (172). Availability of X-ray structures of interacting domains would be helpful to predict druggability with small molecules. Targeting IncRNAs by recruiting epigenetic modifiers may result in specificity issues, because IncRNA-epigenetic modifier interactions are involved in global reprogramming of the genome. Targeting IncRNAs acting by a cis-mechanism would probably result in enhanced specificity compared to those acting by a trans-mechanism. Another critical issue is the poor conservation of the sequences of IncRNAs among different species since they are often derived from intronic or intergenic sequences. This issue has an impact on syngenic metastasis models for evaluation of in vivo anti-metastatic efficacy and for toxicology studies of human IncRNAs in other species. As outlined, metastasis-suppressing or -promoting activity has been described for several IncRNAs. In order to design meaningful clinical studies, information which step(s) of the metastatic cascade are promoted or inhibited by individual IncRNAs would be very helpful. This issue holds true for all IncRNAs discussed in this review.

Nucleic acid-based approaches are under extensive clinical investigation. Two synthetic oligonucleotides have been approved by FDA and numerous ASO-based clinical trials are ongoing (173). At least 25 RNAi-based drug candidates are under clinical evaluation (174). Another lncRNA therapy-related aspect is plasmid-based therapy through expression of diphteria toxin-A in cancer cells under the control of the promoter of H19 IncRNA, which is an oncofetal antigen with strong specificity of expression in tumor cells. This approach is currently in Phase III clinical studies in patients with bladder cancer (175, www.biocancell.com).

The preclinical data should derive a picture, whether IncRNA-related therapeutic approaches will support therapy prior to dissemination, therapy after dissemination prior to formation of overt metastases, therapy after formation of overt metastases or for several of these scenarios (176). Expansion of our knowledge on context and tumor-stage dependent function of IncRNA is a further prerequisite for progress in translational exploitation of IncRNAs for treatment of metastatic disease.

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