## **MALAT1-mediated tumorigenesis**

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#### **1. ABSTRACT**

Functional genomics studies over the past decades have unveiled that the human genome transcribes a large amount of long noncoding RNAs (IncRNAs) which have been implicated in regulation of diverse cellular functions. Dysregulation of IncRNAs are often associated with human diseases including cancer. The metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is among the most abundant and highly conserved IncRNAs. Emerging evidence has indicated that MALAT1 may have complex and extensive functions in the development and progression of cancer. In this review, we first update on the role of MALAT1 in tumorigenesis and then discuss possible molecular mechanisms that underline the MALAT1-mediated gene regulation, leading to cancer invasion and metastasis.

### **2. INTRODUCTION**

Advances in functional genomics have revealed that protein-encoding genes only account for about 2% of the human transcripts whereas the vast majority of these transcripts are non-coding genes, including microRNAs and long non-coding RNAs (IncRNAs) (1). While microRNAs are ~22 nucleotides in length, IncRNAs are arbitrarily defined as RNA molecules with > 200 bp in length. Noncoding transcripts were once regarded as evolutionary junk or transcriptional noise for a long time, however, increasing evidence indicates that non-coding RNAs are emerging as important regulators of gene expression, and are implicated in developmental and tissue specific expression patterns, and human diseases. To date, over 50,000 human IncRNAs have been identified (2). Although IncRNAs can be transcribed by RNA polymerase III (pol III), the most of them are transcribed by RNA polymerase II (pol II) and are polyadenylated (3, 4). Moreover, IncRNAs have greater potential and versatility for both protein and target recognition through their complex secondary and higher order structures (5, 6). Despite being relatively newly discovered, emerging evidence indicates that IncRNAs play an important role in many important biological processes, including cell proliferation (7), survival (8), differentiation (9), organogenesis (10), dosage compensation (11), genomic imprinting (12) and chromatin remodeling (13). New functions of IncRNAs are still being discovered.

MALAT1 (Metastasis-Associated Lung Adenocarcinoma Transcript 1) is one of the most studied



Figure 1. Dates of publications of MALAT1 gene (Thomson Reuters).

IncRNAs (14). According to Thomson statistics, the number of publications on MALAT1 has been steadily increasing from year 2010 to 2015 (Figure 1). In this review, we discuss the latest understanding of the roles of MALAT1 in various aspects of tumorigenesis. We also touch on molecular mechanisms by which MALAT1 regulates tumorigenesis through various mechanisms.

# 3. STRUCTURE AND BIOGENESIS OF MALAT1

MALAT1 (also named NEAT2. HCN. LINC00047, NCRN00047 and PRO2853) is mapped to human chromosome 11q13 (15). MALAT1 RNA is 8.7. kb in length from a single exon, and is predominantly localized to nuclear speckles. MALAT1 was originally identified in a screen for transcripts associated with metastasis and patient survival in non-small cell lung cancer (NSCLC) (14). The half-life of MALAT1 is relatively long, ranging from ~ 9h to > 12h and appears to be unaffected by nuclear RNases or RNA helicases (16), which may contribute to its relative abundance (14). Yet unlike other IncRNAs, mature MALAT1 lacks a poly A tail. It has been shown that MALAT1 carries highly conserved triple helical structures which are capable of protecting its 3' end from 3'-5' exonucleases (17). However, RNase P cleaves the nascent MALAT1 transcript, generating the mature MALAT1 transcript (nuclear-retained MALAT1 as stem-loop structure) and the small cytoplasmic RNA (61-nt tRNA-like ncRNA referred to as mascRNA) (18). Phylogenetic analysis indicates that MALAT1 is highly conserved with up to 90% identity between human and mouse in the last 5 kb of the RNA. Analysis of crystal structure of a 3'-stemloop structure of human MALAT1 indicates that the unique triple-helical structure of the MALAT1 is a key factor responsible for MALAT1 stability (19). In addition, the Drosha-DGCR8 complex can also control the

abundance of MALAT1 by interaction with the 5' end of MALAT1 (20).

MALAT1 is subject to posttranscriptional impacting MALAT1-mediated modifications. thus. cellular function or gene expression. For example, N(6)methyladenosine (m6A) is a reversible and abundant internal modification of mRNAs and IncRNAs with roles in RNA processing, transport, and stability. In this regard, m6A can modify MALAT1 hairpin to increase the accessibility of a U5-tract for recognition and binding by hnRNP C and impact cellular processes (21). Moreover, as an important nuclear protein for pre-mRNA processing, hnRNP C preferentially binds to the m6A-modified hairpin composed of nucleotides 2556~2587 of MALAT1 (22). These findings suggest that with different structures. MALAT1 may be able to exert its specific functions in different cell types, tissues or cellular processes.

## 4. EXPRESSION OF MALAT1 IN CANCER

Although MALAT1 is also expressed in normal tissue (14, 23), its upregulation has been reported in a variety of cancer types through various detection methods. For example, by transcriptomic and genomic analysis, Luo et al., showed that MALAT1 is among several other proteincoding genes overexpressed in human hepatoblastomas (HPBL) versus human hepatocellular carcinomas (HCC) (24). In situ hybridization revealed that MALAT1 is upregulated in endometrial stromal sarcoma as compared with the stroma of normal endometrium (25). The same in situ hybridization assay also showed that MALAT1 is overexpressed in NSCLC (26). Quantitative RT-PCR detected upregulation of MALAT1 in HCC (27) and highgrade osteosarcoma (28). Deep sequencing suggested that MALAT1 is abundantly expressed in primary breast cancer samples (29). Analysis of TCGA RNA-seq data (http://www.cbioportal.org/) for lung cancer reveals that 7% among 517 cases carry MALAT1 upregulation.

More recent studies further support the upregulation of MALAT1 in cancer, including clear cell renal cell carcinoma (30), colorectal cancer (31), gastric cancer (32), colon cancer (33) pancreatic cancer (34-36), bladder cancer (37), glioma (38), myeloma (39), gallbladder cancer (40), lung cancer (41), HR-HPV (+) cervical cancer (42), esophageal squamous cell carcinoma (33, 43), and oral squamous cell carcinoma (44). Of interest, MALAT1 may serve as a prognosis marker in the following cancer types: HCC (27), clear cell renal cell carcinoma (30), colorectal cancer (31), pancreatic cancer (34-36), bladder cancer (37), glioma (38), cervical cancer (45), thoracic esophageal squamous cell (43), prostate cancer (46) and myeloma (47). Moreover, MALAT1 has been shown to be a potential blood-based biomarker for prostate cancer (48) and pancreatic cancer (49). Together, these studies highlight the significance of MALAT1 in cancer (Table 1).

Table 1.	Expression	of MALAT1	in cancer
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Cancer type	Date	Expression	Role of MALAT1	Reference
Lung cancer				
NSCLC	2003	up	Prognostic parameter for survival	(14)
lung squamous cell	2011	up	Associated with a poor prognosis	(26)
brain metastasis NSCLC	2015	up	Promotes brain migration and metastasis by inducing EMT	(41)
liver cancer	2006	up	Risk factor of recurrence after live transplantation	(24)
uterus endometrial stromal sarcoma	2006	up	Regulation of proliferation	(25)
НСС	2007	up	Potential marker for neoplastic cells	(107)
osteosarcoma	2007	up	Prognostic factor	(28, 108)
bladder cancer	2012	up	Promote EMT	(37)
prostate cancer	2013	up	Dignostic/prognostic factor	(48, 50,109)
pancreatic cancer	2014	up	Prognostic factor,	(34-36)
myeloma	2014	up	Predictor of early progression	(47)
colorectal cancer	2014	up	Independent prognostic risk factor	(31, 110)
gastric cancer	2014	up	Potential biomarker	(32)
colon cancer	2014	up	Promotes migration and invasion	(33)
melanoma	2014	up	Promotes migration and metastasis	(39)
gallbladder cancer	2014	up	Promotes proliferation and metastasis	(40)
glioma	2015	up	Independent prognostic predictor	(38)
cervical cancer	2015	up	HR-HPV (+) prognostic	(42, 45)
clear cell renal cell carcinoma	2015	up	Potential prognostic biomarker	(30)
esophageal squamous cell carcinoma	2015	up	Predictor for patient's condition	(111,112)
oral squamous cell carcinoma	2015	up	Regulation of migration and invasion	(44)

## 5. REGULATION OF MALAT1

Although MALT1 is relatively abundant in both normal and cancer cells compared to other IncRNAs, increasing evidence indicates that expression of MALAT1 is regulated by various factors. For example, MALAT1 is upregulated in both TK6 and WTK1 of lymphoblastoid cells at different time by ionizing radiation (50). In human SK-N-SH neuroblastoma cells, MALAT1 levels are upregulated by oxytocin through the binding of the CREB transcription factor to the MALAT1 promoter (51), JMJD1A, a histone H3K9 demethylase, binds to the MALAT1 promoter and demethylates histone H3K9 at the promoter, leading to upregulation of MALAT1 (52). Depletion of TDP-43 expression suppresses MALAT1, whereas TDP-43 overexpression increases MALAT1 (53). On the other hand, protocadherin 10 (PCDH10) suppresses MALAT1 though the Wnt/β-catenin pathway in endometrial cancer (54). In breast cancer cells, 17β-estradiol negatively regulates MALAT1 transcription by a dosedependent (55). Finally, MALAT1 is suppressed by transcription factor SRY-box 17 via the SRY-mediated transcriptional regulation in esophageal cancer (56). Thus, these results demonstrate that expression of MALAT1 is subject to positive or negative regulators.

# 6. REGULATION OF GENE EXPRESSION BY MALAT1

### 6.1. MALAT1-mediated alternative splicing

Higher eukaryotes achieve transcriptome and proteomic complexity by utilizing alternative splicing (AS) of pre-mRNA. AS is regulated by trans-acting protein factors, including the small nuclear ribonucleoproteins (snRNPs), the serine/arginine-rich (SR) family of nuclear phosphoproteins. SR-related proteins. and the heterogeneous nuclear ribonucleoproteins (hnRNPs) (57). SR proteins are regarded as a class of RNA-binding proteins in constitutive splicing. Moreover, AS can recognize *cis*-acting exonic splicing enhancers through their sequence-specific and recruit other splicing factors to facilitate the assembly of the spliceosome (58). However, these splicing factors generally serve as basic machinery. Regulation of AS for a specific set of genes under a give circumstance may require additional factors where IncRNAs may play such a role. In this regard, MALAT1 is identified in nuclear SC35 speckles, including U snRNA-protein complexes (U snRNPs) and SR family splicing regulators. MALAT1 interacts with SR proteins including SRSF1, SRSF2, and SRSF3. MALAT1 can influence the distribution of these and other splicing factors including SF1, U2AF65, SF3a60,

and U2B in nuclear speckle domains; it regulates premRNA processing by modulating the phosphorylation levels of SR proteins (23, 59). In support of the role of MALAT1 in AS, whole genome analysis of breast cancer cells identified multiple mutations in the SRSF1-binding items of MALAT1 (29). Consistent with the reports that translocations and point mutations of MALAT1 have been reported in sarcoma (60) and colorectal cancer cell lines (61), depletion of MALAT1 suppresses the recruitment of SR splicing factors (SF2/ASF, SC35) to the transcription site (62). However, knockout mouse experiments suggest that depletion of MALAT1 does not affect the level of splicing factors or their phosphorylation status, or global effect on alternative splicing; instead it may play a potential cis-regulatory role (63), suggesting that MALAT1 may regulate AS for a specific set of genes in a cell type specific manner.

# 6.2. MALAT1-mediated transcriptional regulation

LncRNAs regulate transcription through various mechanisms (64). For example, IncRNAs may serve as 1) signals for transcription; 2) decoys to titrate transcription factors; 3) guides for chromatinmodifying enzymes to be recruited to target genes and 4) scaffolds to bring together multiple proteins to form functional ribonucleoprotein complexes (65-67). As such. IncRNAs may serve as master gene regulators. In particular, IncRNAs have been implicated in epigenetic regulation of gene expression through which IncRNAs can regulate large numbers of genes (68). For example, HOTAIR is one of the early identified IncRNAs and plays a critical role in cancer through epigenetic regulation mechanisms. HOTAIR is a 2.2. kb gene in the HOXC locus, which, however, can repress transcription in trans of HOXD genes. This repressive action is mediated by the interaction of HOTAIR with the Polycomb Repressive Complex 2 (PRC2) (69). In this regard, MALAT1 regulates the localization of PRC2 through cooperation with aurine up-regulated 1 (TUG1) (70). Moreover, unmethylated PRC2 preferentially interacts with MALAT1 in the nuclear speckles. Importantly, MALAT1 acts as a molecular scaffold to allow gene expression during serum stimulation though promoting the interaction among unmethylated PRC2, E2F, activation-associated histone markers, and the transcriptional coactivator complex. For example, MALAT1 along with NEAT1 has been mapped to hundreds of genomic sites in human cells (71), suggesting that MALAT1 is closely associated with actively transcribed genes. Furthermore, MALAT1 also tends to overlap the enrichment of histone H3K36me2 peaks, a marker of active transcriptional elongation by interacting with the 3' end of the gene body. In multiple myeloma from mesenchymal stem cells, MALAT1 regulates LTBP3 transcription by recruiting Sp1 to the LTBP3 promoter (72). In this way, MALAT1 positively regulates LTBP3 transcription. Interestingly, both genes are closely located on chromosome 11g13.1., which

suggest that MALAT1 may regulate the expression of neighboring genes *in cis*.

Further experiments with RNAi revealed that MALAT1 regulates the expression of a set of genes involved in cellular motility (73). Other genes including those regulated by post-transcriptional mechanism are listed in Table 2. Together, these studies suggest that transcriptional regulation also plays an important role. Since many of these genes are involved in cell migration, invasion and metastasis, it is understandable that upregulation of MALAT1 is often associated with cancer progression. However, it remains to be determined as to how MALAT1 is involved in transcriptional regulation.

# 6.3. MALAT1-mediated post-transcriptional regulation

LncRNAs have complex post-transcriptional regulation function including mRNA stability, mRNA translation, pre-mRNA splicing or protein activities. The major mechanisms of post-transcriptional regulation of MALAT1 include alternative splicing, protein activities and competitive endogenous RNAs (ceRNAs) (74). Since we already discussed the gene splicing function early, we will mainly focus on MALAT1-mediated ceRNA mechanism.

The ceRNA concept was proposed initially for the interaction among microRNAs and proteincoding genes (75) where microRNA response elements (MREs) may serve as letters of a new language. Recent evidence indicates that this can also expand to IncRNAs including MALAT1. Evidently this ceRNA mechanism provides an additional level of post-transcriptional regulation (76, 77). Several recent studies showed that IncRNAs and microRNAs interaction in a reciprocal repression manner (78-81). Through this mechanism, IncRNAs may act as repressor to microRNAs; in contrast, microRNAs may reduce IncRNA expression in an AGO2dependent manner (82, 83). For example, miR-9 targets MALAT1 for degradation in nucleus by directly binding to two microRNA binding sites of MALAT1 sequence at position 1,199 and 6,229, respectively (84). Further, MALAT1 acts as sponge for miR-9 in nucleus of U87MG and L428 cells through Ago2-mediated pathway (84). MALAT1 can also indirectly modulate RBG2 expression via competing with miR-124 to promote tumorigenesis in cervical cancer through the MALAT1-miR-124-RBG2 axis (42).

In addition, reciprocal interaction between MALAT1 and microRNAs are also observed in other types of cancer cells, such as MALAT1 and miR-205 in renal cell carcinoma (85), MALAT1 and miR-140 in glioma endothelial cells (86). By CeRNA mechanism, MALAT1 may de-repress expression of the target genes for the corresponding microRNAs, leading to phenotypic changes such as cell invasion. On the other hand, **Table 2.** Regulation of target protein expression or activity by MALAT1

Effect	Target protein	Regulation mechanism	Reference
down	CA2	Transcriptional regulation	(113)
down	E-cadherin	Transcriptional regulation	(41, 96)
down	HNF5G	Transcriptional regulation	(114)
down	MIA3	Transcriptional regulation	(115)
down	RASSF7	Transcriptional regulation	(116)
down	ROBO2	Transcriptional regulation	(117)
down	HNF4G	Transcriptional regulation	(113)
down	MIA2	Transcriptional regulation	(113)
down	RASSF6	Transcriptional regulation	(113)
down	ROBO1	Transcriptional regulation	(113)
up	ABCA1	Transcriptional regulation	(113)
up	ADAMTS12	Transcriptional regulation	(113)
up	AIM1	Transcriptional regulation	(73)
up	AKAP9	Transcriptional regulation	(110)
up	BMPER	Transcriptional regulation	(113)
up	CDCP1	Transcriptional regulation	(113)
up	COL6A1	Transcriptional regulation	(113)
up	СРМ	Transcriptional regulation	(113)
up	CSF1	Transcriptional regulation	(113)
up	CXCL5	Transcriptional regulation	(113)
up	DRD1	Transcriptional regulation	(113)
up	GPC6	Transcriptional regulation	(113)
up	HMMR	Transcriptional regulation	(73)
up	LAYN	Transcriptional regulation	(73)
up	LPAR1	Transcriptional regulation	(113)
up	LPHN2	Transcriptional regulation	(113)
up	LY6K	Transcriptional regulation	(113)
up	MCAM	Transcriptional regulation	(113)
up	NNMT	Transcriptional regulation	(113)
up	PRKCE	Transcriptional regulation	(113)
up	Slug	Transcriptional regulation	(37)
up	Zb1	Transcriptional regulation	(37)
up	Zb2	Transcriptional regulation	(37)
up	Snail	Transcriptional regulation	(96)
up	vimentin	Transcriptional regulation	(96)
up	MMP9	Transcriptional regulation	(98)
up	PCNA	Transcriptional regulation	(98)

## (Contd..)

## Table 2. (Continued)

Effect	Target	Regulation mechanism	Reference
	protein		
up	LTBP3	Transcriptional regulation	(72)
up	CTHRC1	Post-transcriptional regulation	(73)
up	FHL1	Post-transcriptional regulation	(73)
up	ROD1	Post-transcriptional regulation	(73)
Activation	AKT	Post-translational regulation	(98)
Activation	PI3Kp85α	Post-translational regulation	(98)
Inactivation	β-catenin	Post-translational regulation	(37)

post-transcriptional regulation of MALAT1 by microRNAs such as miR-101 and miR-217 can suppress proliferation, migration, and invasion of ESCC cells (87). Furthermore, MALAT1 can promote clear cell kidney carcinoma proliferation and metastasis through miR-200s (88). miR-125b suppresses bladder cancer development via inhibiting SIRT7 and MALAT1 (89). It appears that interactions between MALAT1 and microRNAs are deeply involved of regulation of malignant phenotypes of cancer. Therefore, MALAT1 has also joined the CeRNA regulatory system through which MALAT1 and microRNAs can interact and negatively regulate each other.

## 7. MALAT1-ASSOCIATED SIGNALING PATHWAYS IN CANCER AND ITS CLINICAL SIGNIFICANCE

## 7.1. Wnt/β-catenin pathway

The Wnt/β-catenin signaling pathway is an important pathway in embryonic development and tumorigenesis (90). MALAT1 has been implicated in the Wnt/β-catenin signaling. For example, re-expression of wnt inhibitor factor 1 (WIF1) can inhibit cell migration by downregulating MALAT1 in a non-canonical Wnt signaling manner in glioblastoma (91). In colorectal cancer, resveratrol can downregulate MALAT1 such that it reduces the nuclear localization of β-catenin and attenuates Wnt/β-catenin signaling, leading to inhibition of invasion and metastasis (92). In endometrioid endometrial carcinoma, PCDH10 suppresses MALAT1 and attenuates Wnt/β-catenin signaling via TCF promoter binding (54). Finally, MALAT1 also promotes EMT by activating Wnt signaling in bladder cancer (37). However, the detailed mechanism of how MALAT1 is involved in Wnt/β-catenin signaling still remains to be determined vet.

## 7.2. Epithelial-to-mesenchymal transition (EMT)

EMT is a fundamental process for distant metastasis during which tumor cells lose their epithelial properties and acquire a fibroblast-like phenotype for tumor invasion and dissemination (93). EMT is an essential process in invasion and metastasis, and is regarded as a major mechanism for cancer metastasis. MALAT1 is involved in EMT-mediated cell migration and invasion in various malignant tumors (94). In bladder cancer, MALAT1 silencing leads to a decrease of ZEB1, ZEB2 and Slug levels, and an increase of E-cadherin levels (37); further, TGF-β can induce MALAT1 expression and promote EMT. For instance, MALAT1 knockdown inhibits TGF-β-induced EMT though suppressor of zeste 12 (suz12) (95). MALAT1 is associated with colon cancer progression by TADC-derived CCL5, whereas blocking MALAT1 significantly reduces CCL5-induced migration and invasion by suppression of Snail (33). Moreover, MALAT1 knockdown significantly suppresses expression of N-cadherin and vimentin, but induces expression of E-cadherin in oral squamous cell carcinoma (OSCC) cell line TSCCA and Tca8113 (44). Similarly, MALAT1 knockdown decreases EMT marker genes expression including Snail, Slug, N-cadherin and vimentin, while it increases E-cadherin expression in pancreatic cancer AsPC-1 and CFPAC-1 cells (34). Overexpression of MALAT1 suppresses E-cadherin expression, promotes vimentin expression and enhances the proliferation, invasion, and metastasis of nasopharyngeal carcinoma CNE-1 cells (96). Of interest, in contrast to its role in breast cancer, knockdown of MALAT1 induces an EMT and enhances breast cancer cell migration and invasion by activating the phosphatidylinositide-3 kinase (PI3K)-AKT pathway (97), but this remains to be confirmed by further studies. In summary, there is a large body of evidence that MALAT1 plays an important role in EMT-mediated program, leading to cell invasion and metastasis.

### 7.3. PI3K/AKT pathway

PI3K/AKT signaling pathway regulates multiple cellular processes such as cell proliferation, survival or migration. Over-activation of this pathway is frequently seen in many human malignancies and it plays a key role in cancer progression. Emerging evidence suggests that MALAT1 plays an oncogenic role through PI3K/AKT pathway. For instance, MALAT1 knockdown significantly suppresses PI3Kp85a and pAKT level in osteosarcoma cells; Ectopic expression of MALAT1 promotes tumor growth and metastasis by activating PI3K/AKT signaling cascade (97). In contrast, knockdown of MALAT1 increases phosphorylated AKT (pS473) levels in breast cancer MDA-MB-231 and MCF-7 cells (97). It remains to be determined whether this is due to cell type specific. In osteosarcoma cells, MALAT1 induces proliferation and metastasis through activation of PI3Kp85a at posttranscriptional level (98). MALAT1 can also regulates AKT activity through the miR-22-3p-CXCR2 axis, leading to aggravating the oxidized low-density lipoprotein (ox-LDL)induced endothelial injury, a process associated with the AKT pathway (99). Given the importance of MALAT1 in various aspects of tumorigenesis cancer, targeting MALAT1 may enhance the AKT pathway-cancer therapy (100).

## 7.4. ERK/MAPK pathway

Extracellularly Regulated Kinase/Mitogen Activated Protein Kinase (ERK/MAPK) signaling pathway is a key regulator of cellular processes such as proliferation, differentiation, development, survival and apoptosis (101). Most functions of ERK/MAPK kinases depend on their ability to phosphorylate multiple target proteins (101). MALAT1 promotes tumor growth and metastasis though activating this signaling cascade (102). In glioma stem cells, knockdown of MALAT1 promotes proliferation in SHG139 cell by activating ERK/MAPK signaling (103). ERK/MAPK pathway is found to be inactivated in the gallbladder cancer SGC-996 and NOZ cells after MALAT1 knockdown. MALAT1 knockdown significantly reduces the expression of phosphorylated MEK1/2, ERK 1/2, MAPK, and JNK 1/2/3, which suggests MALAT1 might promote proliferation and metastasis of gallbladder cancer by activating the ERK/MAPK pathway (40). MALAT1 has also been implicated in retinal endothelial cell function and pathological microvascular growth under diabetic condition by activating p38/MAPK signaling pathway (104).

### 7.5. Angiogenesis

One important aspect of tumorigenesis is tumor angiogenesis. A main driving factor for angiogenesis is hypoxia. In this regard, MALAT1 is often upregulated in cancer cells under hypoxic conditions. For example, hypoxia induces MALAT1 in human neuroblastoma cells whereas MALAT1 suppression reduces expression of fibroblast growth factor 2 (FGF2) which is a well-known growth factor (105). Moreover, conditioned media from neuroblastoma cells transfected with MALAT1 siRNA causes significantly less endothelial cell migration, invasion and vasculature formation. Finally, addition of recombinant FGF2 to the cell culture media reversed the effects of MALAT1 siRNA on vasculature formation (105). Consistent with this finding, MALAT1 expression is also significantly increased by hypoxia in endothelial cells. In vivo studies indicate that genetic ablation of MALAT1 inhibits proliferation of endothelial cells (106). Thus, the MALAT1 level appears to control the balance between proliferative and migratory phenotype of endothelial cells although the underlying mechanism remains to be determined yet.

### 8. SUMMARY

MALAT1 is a multi-functional IncRNAs, which might be attributed to its relative large RNA molecule and highly structural nature. It is evident now that MALAT1 plays an oncogenic role through regulation of gene expression or various pathways. Although there are many ways that MALAT1 can impact gene expression, our discussion mainly focuses on transcriptional/posttranscriptional regulation, alternative splicing and CeRNA mechanisms as outlined in Figure 2. Evidently, these mechanisms are often overlapped through cross-talk and



Figure 2. MALAT1-mediated gene regulation leading to tumorigenesis. MALAT1 folding structures are based on LNCipedia (http://www.incipedia.org).

thus, it may be difficult to delineate them. Nevertheless, a consequence of these actions is increased invasion and metastasis for cancer cells. Future work will be focused on dissection of the underlying mechanism by which MALAT1 promotes tumorigenesis. For example, it would be interesting to determine how hypoxia induces MALAT1 which causes migratory phenotype endothelial cells. Finally, given its clinical significance, it would be also interesting to determine whether MALAT1 serve as a potential therapeutic target.

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## **10. REFERENCES**

- L. D. Stein: Human genome: end of the beginning. *Nature*, 431(7011), 915-6 (2004) DOI: 10.1038/431915a
- C. Xie, J. Yuan, H. Li, M. Li, G. Zhao, D. Bu, W. Zhu, W. Wu, R. Chen and Y. Zhao: NONCODEv4: exploring the world of long non-coding RNA genes. *Nucleic Acids Res*, 42(Database issue), D98-103 (2014) DOI: 10.1093/nar/gkt1222
- J. Cheng, P. Kapranov, J. Drenkow, S. Dike, S. Brubaker, S. Patel, J. Long, D. Stern, H. Tammana, G. Helt, V. Sementchenko, A. Piccolboni, S. Bekiranov, D. K. Bailey, M. Ganesh, S. Ghosh, I. Bell, D. S. Gerhard and T. R. Gingeras: Transcriptional maps

of 10 human chromosomes at 5-nucleotide resolution. *Science*, 308(5725), 1149-54 (2005)

DOI: 10.1126/science.1108625

- Q. Wu, Y. C. Kim, J. Lu, Z. Xuan, J. Chen, Y. Zheng, T. Zhou, M. Q. Zhang, C. I. Wu and S. M. Wang: Poly A- transcripts expressed in HeLa cells. *PLoS One*, 3(7), e2803 (2008) DOI: 10.1371/journal.pone.0002803
- 5. P. J. Batista and H. Y. Chang: Long noncoding RNAs: cellular address codes in development and disease. *Cell*, 152(6), 1298-307 (2013) DOI: 10.1016/j.cell.2013.02.012
- M. Guttman and J. L. Rinn: Modular regulatory principles of large non-coding RNAs. *Nature*, 482(7385), 339-46 (2012) DOI: 10.1038/nature10887
- C. P. Ponting, P. L. Oliver and W. Reik: Evolution and functions of long noncoding RNAs. *Cell*, 136(4), 629-41 (2009) DOI: 10.1016/j.cell.2019.02.006
- J. Shen, A. B. Siegel, H. Remotti, Q. Wang, Y. Shen and R. M. Santella: Exploration of Deregulated Long Non-Coding RNAs in Association with Hepatocarcinogenesis and Survival. *Cancers (Basel)*, 7(3), 1847-62 (2015)

DOI: 10.3390/cancers7030865

9. M. R. Stratton, P. J. Campbell and P. A. Futreal: The cancer genome. *Nature*, 458(7239), 719-24 (2009) DOI: 10.1038/nature07943

- 10. P. Grote and B. G. Herrmann: Long noncoding RNAs in organogenesis: making the difference. *Trends Genet*, 31(6), 329-35 DOI: 10.1016/j.tig.2015.02.002
- D. U. Menon and V. H. Meller: Identification of the Drosophila X chromosome: The long and short of it. *RNA Biol*, 0 (2015) DOI: 10.1080/15476286.2015.1086864
- C. Kanduri: Long noncoding RNAs: Lessons from genomic imprinting. *Biochim Biophys Acta* (2015) DOI: 10.1016/j.bbagrm.2015.05.006
- T. Nagano and P. Fraser: No-nonsense functions for long noncoding RNAs. *Cell*, 145(2), 178-81 (2011) DOI: 10.1016/j.cell.2011.03.014
- P. Ji, S. Diederichs, W. Wang, S. Boing, R. Metzger, P. M. Schneider, N. Tidow, B. Brandt, H. Buerger, E. Bulk, M. Thomas, W. E. Berdel, H. Serve and C. Muller-Tidow: MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene*, 22(39), 8031-41 (2003)

DOI: 10.1038/sj.onc.1206928

 M. van Asseldonk, M. Schepens, D. de Bruijn, B. Janssen, G. Merkx and A. Geurts van Kessel: Construction of a 350-kb sequenceready 11q13 cosmid contig encompassing the markers D11S4933 and D11S546: mapping of 11 genes and 3 tumor-associated translocation breakpoints. *Genomics*, 66(1), 35-42 (2000)

DOI: 10.1006/geno.2000.6.194

- H. Tani, Y. Nakamura, K. Ijiri and N. Akimitsu: Stability of MALAT-1, a nuclear long noncoding RNA in mammalian cells, varies in various cancer cells. *Drug Discov Ther*, 4(4), 235-9 (2010)
- J. E. Wilusz, C. K. JnBaptiste, L. Y. Lu, C. D. Kuhn, L. Joshua-Tor and P. A. Sharp: A triple helix stabilizes the 3' ends of long noncoding RNAs that lack poly(A) tails. *Genes Dev*, 26(21), 2392-407 (2012) DOI: 10.1.101/gad.204438.112
- J. E. Wilusz, S. M. Freier and D. L. Spector: 3' end processing of a long nuclear-retained noncoding RNA yields a tRNA-like cytoplasmic RNA. *Cell*, 135(5), 919-32 (2008)

DOI: 10.1016/j.cell.2008.10.012

- J. A. Brown, D. Bulkley, J. Wang, M. L. Valenstein, T. A. Yario, T. A. Steitz and J. A. Steitz: Structural insights into the stabilization of MALAT1 noncoding RNA by a bipartite triple helix. *Nat Struct Mol Biol*, 21(7), 633-40 (2014)
   DOI: 10.1038/nsmb.2844
- S. Macias, M. Plass, A. Stajuda, G. Michlewski, E. Eyras and J. F. Caceres: DGCR8 HITS-CLIP reveals novel functions for the Microprocessor. *Nat Struct Mol Biol*, 19(8), 760-6 (2012) DOI: 10.1038/nsmb.2344
- K. I. Zhou, M. Parisien, Q. Dai, N. Liu, L. Diatchenko, J. R. Sachleben and T. Pan: N-Methyladenosine Modification in a Long Noncoding RNA Hairpin Predisposes Its Conformation to Protein Binding. *J Mol Biol* (2015) DOI: 10.1016/j.jmb.2015.08.021
- 22. N. Liu, Q. Dai, G. Zheng, C. He, M. Parisien and T. Pan: N(6)-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. *Nature*, 518(7540), 560-4 (2015) DOI: 10.1038/nature14234
- J. N. Hutchinson, A. W. Ensminger, C. M. Clemson, C. R. Lynch, J. B. Lawrence and A. Chess: A screen for nuclear transcripts identifies two linked noncoding RNAs associated with SC35 splicing domains. *BMC Genomics*, 8, 39 (2007) DOI: 10.1186/1471-2164-8-39
- J. H. Luo, B. Ren, S. Keryanov, G. C. Tseng, U. N. Rao, S. P. Monga, S. Strom, A. J. Demetris, M. Nalesnik, Y. P. Yu, S. Ranganathan and G. K. Michalopoulos: Transcriptomic and genomic analysis of human hepatocellular carcinomas and hepatoblastomas. *Hepatology*, 44(4), 1012-24 (2006) DOI: 10.1002/hep.21328
- K. Yamada, J. Kano, H. Tsunoda, H. Yoshikawa, C. Okubo, T. Ishiyama and M. Noguchi: Phenotypic characterization of endometrial stromal sarcoma of the uterus. *Cancer Sci*, 97(2), 106-12 (2006) DOI: 10.1111/j.1349-7006.2006.00147x
- L. H. Schmidt, T. Spieker, S. Koschmieder, S. Schaffers, J. Humberg, D. Jungen, E. Bulk, A. Hascher, D. Wittmer, A. Marra, L. Hillejan,

K. Wiebe, W. E. Berdel, R. Wiewrodt and C. Muller-Tidow: The long noncoding MALAT-1 RNA indicates a poor prognosis in non-small cell lung cancer and induces migration and tumor growth. *J Thorac Oncol*, 6(12), 1984-92 (2011)

DOI: 10.1097/JTO.0b013e3182307eac

 M. C. Lai, Z. Yang, L. Zhou, Q. Q. Zhu, H. Y. Xie, F. Zhang, L. M. Wu, L. M. Chen and S. S. Zheng: Long non-coding RNA MALAT-1 overexpression predicts tumor recurrence of hepatocellular carcinoma after liver transplantation. *Med Oncol*, 29(3), 1810-6 (2012)

DOI: 10.1007/s12032-011-0004-z

- J. Fellenberg, L. Bernd, G. Delling, D. Witte and A. Zahlten-Hinguranage: Prognostic significance of drug-regulated genes in highgrade osteosarcoma. *Mod Pathol*, 20(10), 1085-94 (2007) DOI: 10.1038/modpathol.3800937
- 29. M. J. Ellis, L. Ding, D. Shen, J. Luo, V. J. Suman, J. W. Wallis, B. A. Van Tine, J. Hoog, R. J. Goiffon, T. C. Goldstein, S. Ng, L. Lin, R. Crowder, J. Snider, K. Ballman, J. Weber, K. Chen, D. C. Koboldt, C. Kandoth, W. S. Schierding, J. F. McMichael, C. A. Miller, C. Lu, C. C. Harris, M. D. McLellan, M. C. Wendl, K. DeSchryver, D. C. Allred, L. Esserman, G. Unzeitig, J. Margenthaler, G. V. Babiera, P. K. Marcom, J. M. Guenther, M. Leitch, K. Hunt, J. Olson, Y. Tao, C. A. Maher, L. L. Fulton, R. S. Fulton, M. Harrison, B. Oberkfell, F. Du, R. Demeter, T. L. Vickery, A. Elhammali, H. Piwnica-Worms, S. McDonald, M. Watson, D. J. Dooling, D. Ota, L. W. Chang, R. Bose, T. J. Lev, D. Piwnica-Worms, J. M. Stuart, R. K. Wilson and E. R. Mardis: Whole-genome analysis informs breast cancer response to aromatase inhibition. Nature, 486(7403), 353-60 (2012)

DOI: 10.1038/nature11143

- H. M. Zhang, F. Q. Yang, S. J. Chen, J. Che and J. H. Zheng: Upregulation of long noncoding RNA MALAT1 correlates with tumor progression and poor prognosis in clear cell renal cell carcinoma. *Tumour Biol*, 36(4), 2947-55 (2015) DOI: 10.1007/s13277-014-2925-6
- H. T. Zheng, D. B. Shi, Y. W. Wang, X. X. Li, Y. Xu, P. Tripathi, W. L. Gu, G. X. Cai and S.

J. Cai: High expression of IncRNA MALAT1 suggests a biomarker of poor prognosis in colorectal cancer. *Int J Clin Exp Pathol*, 7(6), 3174-81 (2014)

- Y. Okugawa, Y. Toiyama, K. Hur, S. Toden, S. Saigusa, K. Tanaka, Y. Inoue, Y. Mohri, M. Kusunoki, C. R. Boland and A. Goel: Metastasis-associated long non-coding RNA drives gastric cancer development and promotes peritoneal metastasis. *Carcinogenesis*, 35(12), 2731-9 (2014) DOI: 10.1093/carcin/bgu200
- J. Y. Kan, D. C. Wu, F. J. Yu, C. Y. Wu, Y. W. Ho, Y. J. Chiu, S. F. Jian, J. Y. Hung, J. Y. Wang and P. L. Kuo: Chemokine (C-C Motif) Ligand 5 is Involved in Tumor-Associated Dendritic Cell-Mediated Colon Cancer Progression Through Non-Coding RNA MALAT-1. *J Cell Physiol*, 230(8), 1883-94 (2015) DOI: 10.1002/jcp.24918
- F. Jiao, H. Hu, C. Yuan, L. Wang, W. Jiang, Z. Jin, Z. Guo and L. Wang: Elevated expression level of long noncoding RNA MALAT-1 facilitates cell growth, migration and invasion in pancreatic cancer. *Oncol Rep*, 32(6), 2485-92 (2014) DOI: 10.3892/or.2014.3.518
- J. H. Liu, G. Chen, Y. W. Dang, C. J. Li and D. Z. Luo: Expression and prognostic significance of IncRNA MALAT1 in pancreatic cancer tissues. *Asian Pac J Cancer Prev*, 15(7), 2971-7 (2014) DOI: 10.7314/APJCP.2014.15.7.2971
- 36. E. J. Pang, R. Yang, X. B. Fu and Y. F. Liu: Overexpression of long non-coding RNA MALAT1 is correlated with clinical progression and unfavorable prognosis in pancreatic cancer. *Tumour Biol*, 36(4), 2403-7 (2015) DOI: 10.1007/s13277-014-2850-8
- L. Ying, Q. Chen, Y. Wang, Z. Zhou, Y. Huang and F. Qiu: Upregulated MALAT-1 contributes to bladder cancer cell migration by inducing epithelial-to-mesenchymal transition. *Mol Biosyst*, 8(9), 2289-94 (2012) DOI: 10.1039/c2mb25070e
- K. X. Ma, H. J. Wang, X. R. Li, T. Li, G. Su, P. Yang and J. W. Wu: Long noncoding RNA MALAT1 associates with the malignant status and poor prognosis in glioma. *Tumour Biol*, 36(5), 3355-9 (2015) DOI: 10.1007/s13277-014-2969-7

- Y. Tian, X. Zhang, Y. Hao, Z. Fang and Y. He: Potential roles of abnormally expressed long noncoding RNA UCA1 and Malat-1 in metastasis of melanoma. *Melanoma Res*, 24(4), 335-41 (2014) DOI: 10.1097/cmr.0000000000000080
- X. S. Wu, X. A. Wang, W. G. Wu, Y. P. Hu, M. L. Li, Q. Ding, H. Weng, Y. J. Shu, T. Y. Liu, L. Jiang, Y. Cao, R. F. Bao, J. S. Mu, Z. J. Tan, F. Tao and Y. B. Liu: MALAT1 promotes the proliferation and metastasis of gallbladder cancer cells by activating the ERK/MAPK pathway. *Cancer Biol Ther*, 15(6), 806-14 (2014)

DOI: 10.4161/cbt.28584

41. L. Shen, L. Chen, Y. Wang, X. Jiang, H. Xia and Z. Zhuang: Long noncoding RNA MALAT1 promotes brain metastasis by inducing epithelial-mesenchymal transition in lung cancer. *J Neurooncol*, 121(1), 101-8 (2015)

DOI: 10.1007/s11060-014-1613-0

- 42. S. Liu, L. Song, S. Zeng and L. Zhang: MALAT1-miR-124-RBG2 axis is involved in growth and invasion of HR-HPV-positive cervical cancer cells. *Tumour Biol* (2015) DOI: 10.1007/s13277-015-3732-4
- X. Cao, R. Zhao, Q. Chen, Y. Zhao, B. Zhang, Y. Zhang, J. Yu, G. Han, W. Cao, J. Li and X. Chen: MALAT1 might be a predictive marker of poor prognosis in patients who underwent radical resection of middle thoracic esophageal squamous cell carcinoma. *Cancer Biomark* (2015) DOI: 10.3233/cbm-150513
- X. Zhou, S. Liu, G. Cai, L. Kong, T. Zhang, Y. Ren, Y. Wu, M. Mei, L. Zhang and X. Wang: Long Non Coding RNA MALAT1 Promotes Tumor Growth and Metastasis by inducing Epithelial-Mesenchymal Transition in Oral Squamous Cell Carcinoma. *Sci Rep*, 5, 15972 (2015)

DOI: 10.1038/srep15972

- 45. L. Yang, H. S. Bai, Y. Deng and L. Fan: High MALAT1 expression predicts a poor prognosis of cervical cancer and promotes cancer cell growth and invasion. *Eur Rev Med Pharmacol Sci*, 19(17), 3187-93 (2015)
- D. Wang, L. Ding, L. Wang, Y. Zhao, Z. Sun, R. J. Karnes, J. Zhang and H. Huang: LncRNA MALAT1 enhances oncogenic activities of

EZH2 in castration-resistant prostate cancer. *Oncotarget* (2015) DOI: 10.18632/oncotarget.5728

- 47. S. F. Cho, Y. C. Chang, C. S. Chang, S. F. Lin, Y. C. Liu, H. H. Hsiao, J. G. Chang and T. C. Liu: MALAT1 long non-coding RNA is overexpressed in multiple myeloma and may serve as a marker to predict disease progression. *BMC Cancer*, 14, 809 (2014) DOI: 10.1186/1471-2407-14-809
- S. Ren, F. Wang, J. Shen, Y. Sun, W. Xu, J. Lu, M. Wei, C. Xu, C. Wu, Z. Zhang, X. Gao, Z. Liu, J. Hou, J. Huang and Y. Sun: Long non-coding RNA metastasis associated in lung adenocarcinoma transcript 1 derived miniRNA as a novel plasma-based biomarker for diagnosing prostate cancer. *Eur J Cancer*, 49(13), 2949-59 (2013) DOI: 10.1016/j.ejca.2013.04.026
- 49. T. Kishikawa, M. Otsuka, M. Ohno, T. Yoshikawa, A. Takata and K. Koike: Circulating RNAs as new biomarkers for detecting pancreatic cancer. *World J Gastroenterol*, 21(28), 8527-40 (2015) DOI: 10.3784/wjg.v21.i28.8527
- 50. M. A. Chaudhry: Expression pattern of small nucleolar RNA host genes and long noncoding RNA in X-rays-treated lymphoblastoid cells. *Int J Mol Sci*, 14(5), 9099-110 (2013) DOI: 10.3390/ijms14059099
- T. A. Koshimizu, Y. Fujiwara, N. Sakai, K. Shibata and H. Tsuchiya: Oxytocin stimulates expression of a noncoding RNA tumor marker in a human neuroblastoma cell line. *Life Sci*, 86(11-12), 455-60 (2010) DOI: 10.1016/j.lfs.2010.02.001
- 52. A. E. Tee, D. Ling, C. Nelson, B. Atmadibrata, M. E. Dinger, N. Xu, T. Mizukami, P. Y. Liu, B. Liu, B. Cheung, E. Pasquier, M. Haber, M. D. Norris, T. Suzuki, G. M. Marshall and T. Liu: The histone demethylase JMJD1A induces cell migration and invasion by up-regulating the expression of the long noncoding RNA MALAT1. Oncotarget, 5(7), 1793-804 (2014) DOI: 10.118632/oncotarget.1785
- F. Guo, F. Jiao, Z. Song, S. Li, B. Liu, H. Yang, Q. Zhou and Z. Li: Regulation of MALAT1 expression by TDP43 controls the migration and invasion of non-small cell lung cancer cells *in vitro*. *Biochem Biophys Res Commun*, 465(2), 293-8 (2015)

DOI: 10.1016/j.bbrc.2015.08.027

- Y. Zhao, Y. Yang, J. Trovik, K. Sun, L. Zhou, P. Jiang, T. S. Lau, E. A. Hoivik, H. B. Salvesen, H. Sun and H. Wang: A novel wnt regulatory axis in endometrioid endometrial cancer. *Cancer Res*, 74(18), 5103-17 (2014) DOI: 10.1158/0008-5472.can-14-0427
- 55. Z. Zhao, C. Chen, Y. Liu and C. Wu: 17beta-Estradiol treatment inhibits breast cell proliferation, migration and invasion by decreasing MALAT-1 RNA level. *Biochem Biophys Res Commun*, 445(2), 388-93 (2014) DOI: 10.1016/j.bbrc.2014.02.006
- I. Y. Kuo, C. C. Wu, J. M. Chang, Y. L. Huang, C. H. Lin, J. J. Yan, B. S. Sheu, P. J. Lu, W. L. Chang, W. W. Lai and Y. C. Wang: Low SOX17 expression is a prognostic factor and drives transcriptional dysregulation and esophageal cancer progression. *Int J Cancer*, 135(3), 563-73 (2014) DOI: 10.1002/ijc.28695
- B. J. Blencowe: Alternative splicing: new insights from global analyses. *Cell*, 126(1), 37-47 (2006) DOI: 10.1016/j.cell.2006.06.023
- 58. S. Lin and X. D. Fu: SR proteins and related factors in alternative splicing. *Adv Exp Med Biol*, 623, 107-22 (2007)
- M. L. Anko and K. M. Neugebauer: Long noncoding RNAs add another layer to premRNA splicing regulation. *Mol Cell*, 39(6), 833-4 (2010) DOI: 10.1016/j.molcel.2010.09.003
- 60. V. Rajaram, S. Knezevich, K. E. Bove, A. Perry and J. D. Pfeifer: DNA sequence of the translocation breakpoints in undifferentiated embryonal sarcoma arising in mesenchymal hamartoma of the liver harboring the t(11;19)(q11;q13.4.) translocation. *Genes Chromosomes Cancer*, 46(5), 508-13 (2007) DOI: 10.1002/gcc.20437
- C. Xu, M. Yang, J. Tian, X. Wang and Z. Li: MALAT-1: a long non-coding RNA and its important 3' end functional motif in colorectal cancer metastasis. *Int J Oncol*, 39(1), 169-75 (2011)

DOI: 10.3892/ijo.2011.1007

62. D. Bernard, K. V. Prasanth, V. Tripathi, S. Colasse, T. Nakamura, Z. Xuan, M. Q. Zhang, F. Sedel, L. Jourdren, F. Coulpier, A. Triller, D. L.

Spector and A. Bessis: A long nuclear-retained non-coding RNA regulates synaptogenesis by modulating gene expression. *Embo j*, 29(18), 3082-93 (2010)

DOI: 10.1038/emboj.2010.199

- B. Zhang, G. Arun, Y. S. Mao, Z. Lazar, G. Hung, G. Bhattacharjee, X. Xiao, C. J. Booth, J. Wu, C. Zhang and D. L. Spector: The IncRNA Malat1 is dispensable for mouse development but its transcription plays a cis-regulatory role in the adult. *Cell Rep*, 2(1), 111-23 (2012) DOI: 10.1016/j.celrep.2012.06.003
- 64. X. Wang, X. Song, C. K. Glass and M. G. Rosenfeld: The long arm of long noncoding RNAs: roles as sensors regulating gene transcriptional programs. *Cold Spring Harb Perspect Biol*, 3(1), a003756 (2011) DOI: 10.1101/cshperspect.a003756
- 65. T. R. Mercer, M. E. Dinger and J. S. Mattick: Long non-coding RNAs: insights into functions. *Nature reviews. Genetics*, 10(3), 155-9 (2009) DOI: 10.1038/nrg2521
- K. C. Wang and H. Y. Chang: Molecular Mechanisms of Long Noncoding RNAs. *Molecular cell*, 43(6), 904-14 (2011) DOI: 10.1016/j.molcel.2011.08.018
- I. Ulitsky and D. P. BarTel: lincRNAs: Genomics, Evolution, and Mechanisms. *Cell*, 154(1), 26-46 (2013) DOI: 10.1016/j.cell.2013.06.020
- J. T. Lee: Epigenetic regulation by long noncoding RNAs. *Science*, 338(6113), 1435-9 (2012) DOI: 10.1126/science.1231776
- M. Takagi, M. J. Absalon, K. G. McLure and M. B. Kastan: Regulation of p53 translation and induction after DNA damage by ribosomal protein L26 and nucleolin. *Cell*, 123(1), 49-63 (2005) DOI: 10.1016/j.cell.2005.07.034
- L. Yang, C. Lin, W. Liu, J. Zhang, K. A. Ohgi, J. D. Grinstein, P. C. Dorrestein and M. G. Rosenfeld: ncRNA- and Pc2 methylationdependent gene relocation between nuclear structures mediates gene activation programs. *Cell*, 147(4), 773-88 (2011) DOI: 10.1016/j.cell.2011.08.054
- J. A. West, C. P. Davis, H. Sunwoo, M. D. Simon, R. I. Sadreyev, P. I. Wang, M. Y. Tolstorukov and R. E. Kingston: The long

noncoding RNAs NEAT1 and MALAT1 bind active chromatin sites. *Mol Cell*, 55(5), 791-802 (2014) DOI: 10.1016/j.molcel.2014.07.012

- B. Li, P. Chen, J. Qu, L. Shi, W. Zhuang, J. Fu, J. Li, X. Zhang, Y. Sun and W. Zhuang: Activation of LTBP3 gene by a long noncoding RNA (IncRNA) MALAT1 transcript in mesenchymal stem cells from multiple myeloma. *J Biol Chem*, 289(42), 29365-75 (2014) DOI: 10.1074/jbc.M114.572693
- K. Tano, R. Mizuno, T. Okada, R. Rakwal, J. Shibato, Y. Masuo, K. Ijiri and N. Akimitsu: MALAT-1 enhances cell motility of lung adenocarcinoma cells by influencing the expression of motility-related genes. *FEBS Lett*, 584(22), 4575-80 (2010) DOI: 10.1016/j.febslet.2010.10.008
- 74. X. Shi, M. Sun, Y. Wu, Y. Yao, H. Liu, G. Wu, D. Yuan and Y. Song: Post-transcriptional regulation of long noncoding RNAs in cancer. *Tumour Biol*, 36(2), 503-13 (2015) DOI: 10.1007/s13277-015-3106-y
- L. Salmena, L. Poliseno, Y. Tay, L. Kats and P. P. Pandolfi: A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? *Cell*, 146(3), 353-8 (2011) DOI: 10.1016/j.cell.2011.07.014
- A. L. Sarver and S. Subramanian: Competing endogenous RNA database. *Bioinformation*, 8(15), 731-3 (2012) DOI: 10.6026/97320630008731
- M. Cesana, D. Cacchiarelli, I. Legnini, T. Santini, O. Sthandier, M. Chinappi, A. Tramontano and I. Bozzoni: A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA. *Cell*, 147(2), 358-69 (2011) DOI: 10.1016/j.cell.2011.09.028
- J. Li, J. Yang, P. Zhou, Y. Le and Z. Gong: (The biological functions and regulations of competing endogenous RNA). *Yi Chuan*, 37(8), 756-64 (2015) DOI: 10.16288/j.yczz.15-073
- 79. R. Sen, S. Ghosal, S. Das, S. Balti and J. Chakrabarti: Competing endogenous RNA: the key to posttranscriptional regulation. *ScientificWorldJournal*, 2014, 896206 (2014) DOI: 10.1155/2014/896206
- 80. R. O. Bak and J. G. Mikkelsen: miRNA

sponges: soaking up miRNAs for regulation of gene expression. *Wiley Interdiscip Rev RNA*, 5(3), 317-33 (2014) DOI: 10.1002/wrna.1213

- T. Xia, S. Chen, Z. Jiang, Y. Shao, X. Jiang, P. Li, B. Xiao and J. Guo: Long noncoding RNA FER1L4 suppresses cancer cell growth by acting as a competing endogenous RNA and regulating PTEN expression. *Sci Rep*, 5, 13445 (2015) DOI: 10.1038/srep13445
- S. Jalali, D. Bhartiya, M. K. Lalwani, S. Sivasubbu and V. Scaria: Systematic transcriptome wide analysis of IncRNA-miRNA interactions. *PLoS One*, 8(2), e53823 (2013)
   DOI: 10.1371/journal.pone.0053823

Z. Zhang, Z. Zhu, K. Watabe, X. Zhang, C. Bai, M. Xu, F. Wu and Y. Y. Mo: Negative regulation of IncRNA GAS5 by miR-21. *Cell Death Differ*, 20(11), 1558-68 (2013) DOI: 10.1038/cdd.2013.1.10

- 84. E. Leucci, F. Patella, J. Waage, K. Holmstrom, M. Lindow, B. Porse, S. Kauppinen and A. H. Lund: microRNA-9 targets the long noncoding RNA MALAT1 for degradation in the nucleus. *Sci Rep*, 3, 2535 (2013) DOI: 10.1038/srep02535
- H. Hirata, Y. Hinoda, V. Shahryari, G. Deng, K. Nakajima, Z. L. Tabatabai, N. Ishii and R. Dahiya: Long Noncoding RNA MALAT1 Promotes Aggressive Renal Cell Carcinoma through Ezh2 and Interacts with miR-205. *Cancer Res*, 75(7), 1322-31 (2015) DOI: 10.1158/0008-5472.can-14-2931
- J. Ma, P. Wang, Y. Yao, Y. Liu, Z. Li, X. Liu, Z. Li, X. Zhao, Z. Xi, H. Teng, J. Liu and Y. Xue: Knockdown of long non-coding RNA MALAT1 increases the blood-tumor barrier permeability by up-regulating miR-140. *Biochim Biophys Acta* (2015) DOI: 10.1016/j.bbagrm.2015.11.008
- 87. L. Lu, F. Luo, Y. Liu, X. Liu, L. Shi, X. Lu and Q. Liu: Posttranscriptional silencing of the IncRNA MALAT1 by miR-217 inhibits the epithelialmesenchymal transition via enhancer of zeste homolog 2 in the malignant transformation of HBE cells induced by cigarette smoke extract. *Toxicol Appl Pharmacol*, 289(2), 276-85 (2015)

DOI: 10.1016/j.taap.2015.09.016

88. H. Xiao, K. Tang, P. Liu, K. Chen, J. Hu, J. Zeng, W. Xiao, G. Yu, W. Yao, H. Zhou, H. Li, Y. Pan, A. Li, Z. Ye, J. Wang, H. Xu and Q. Huang: LncRNA MALAT1 functions as a competing endogenous RNA to regulate ZEB2 expression by sponging miR-200s in clear cell kidney carcinoma. *Oncotarget*, 6(35), 38005-15 (2015)

DOI: 10.18632/oncotarget.5357

- Y. Han, Y. Liu, H. Zhang, T. Wang, R. Diao, Z. Jiang, Y. Gui and Z. Cai: Hsa-miR-125b suppresses bladder cancer development by down-regulating oncogene SIRT7 and oncogenic long non-coding RNA MALAT1. *FEBS Lett*, 587(23), 3875-82 (2013)
- A. Gupta, A. Verma, A. K. Mishra, G. Wadhwa, S. K. Sharma and C. K. Jain: The Wnt pathway: emerging anticancer strategies. *Recent Pat Endocr Metab Immune Drug Discov*, 7(2), 138-47 (2013) DOI: 10.2174/1872214811307020007
- I. Vassallo, P. Zinn, M. Lai, P. Rajakannu, M. F. Hamou and M. E. Hegi: WIF1 re-expression in glioblastoma inhibits migration through attenuation of non-canonical WNT signaling by downregulating the IncRNA MALAT1. *Oncogene* (2015) DOI: 10.1038/onc.2015.61
- Q. Ji, X. Liu, X. Fu, L. Zhang, H. Sui, L. Zhou, J. Sun, J. Cai, J. Qin, J. Ren and Q. Li: Resveratrol inhibits invasion and metastasis of colorectal cancer cells via MALAT1 mediated Wnt/beta-catenin signal pathway. *PLoS One*, 8(11), e78700 (2013) DOI: 10.1371/journal.pone.0078700
- 93. M. Guarino, B. Rubino and G. Ballabio: The role of epithelial-mesenchymal transition in cancer pathology. *Pathology*, 39(3), 305-18 (2007)

DOI: 10.1080/00313020701329914

94. B. Baum, J. Settleman and M. P. Quinlan: Transitions between epithelial and mesenchymal states in development and disease. *Semin Cell Dev Biol*, 19(3), 294-308 (2008)

DOI: 10.1016/j.semcdb.2008.02.001

 Y. Fan, B. Shen, M. Tan, X. Mu, Y. Qin, F. Zhang and Y. Liu: TGF-beta-induced upregulation of malat1 promotes bladder cancer metastasis by associating with suz12. *Clin Cancer Res*, 20(6), 1531-41 (2014) DOI: 10.1158/1078-0432.ccr-13-1455

- 96. L. Xie, Z. Hu, X. Wang and Z. Li: (Expression of long noncoding RNA MALAT1 gene in human nasopharyngeal carcinoma cell lines and its biological significance). *Nan Fang Yi Ke Da Xue Xue Bao*, 33(5), 692-7 (2013) DOI: 10.3969/j.issn.1673-4254.2013.05.13
- 97. S. Xu, S. Sui, J. Zhang, N. Bai, Q. Shi, G. Zhang, S. Gao, Z. You, C. Zhan, F. Liu and D. Pang: Downregulation of long noncoding RNA MALAT1 induces epithelial-to-mesenchymal transition via the PI3K-AKT pathway in breast cancer. *Int J Clin Exp Pathol*, 8(5), 4881-91 (2015)
- 98. Y. Dong, G. Liang, B. Yuan, C. Yang, R. Gao and X. Zhou: MALAT1 promotes the proliferation and metastasis of osteosarcoma cells by activating the PI3K/Akt pathway. *Tumour Biol*, 36(3), 1477-86 (2015) DOI: 10.1007/s13277-014-2631-4
- 99. Y. Tang, X. Jin, Y. Xiang, Y. Chen, C. X. Shen, Y. C. Zhang and Y. G. Li: The IncRNA MALAT1 protects the endothelium against ox-LDL-induced dysfunction via upregulating the expression of the miR-22-3p target genes CXCR2 and AKT. *FEBS Lett*, 589(20 Pt B), 3189-96 (2015) DOI: 10.1016/j.febslet.2015.08.046
- 100. M. Martini, M. C. De Santis, L. Braccini, F. Gulluni and E. Hirsch: PI3K/AKT signaling pathway and cancer: an updated review. *Ann Med*, 46(6), 372-83 (2014) DOI: 10.3109/07853890.2014.912836
- 101. Y. D. Shaul and R. Seger: The MEK/ERK cascade: from signaling specificity to diverse functions. *Biochim Biophys Acta*, 1773(8), 1213-26 (2007) DOI: 10.1016/j.bbamcr.2006.10.005
- 102. A. De Luca, M. R. Maiello, A. D'Alessio, M. Pergameno and N. Normanno: The RAS/ RAF/MEK/ERK and the PI3K/AKT signalling pathways: role in cancer pathogenesis and implications for therapeutic approaches. *Expert Opin Ther Targets*, 16 Suppl 2, S17-27 (2012)

DOI: 10.1517/14728222.2011.639361

103. Y. Han, L. Zhou, T. Wu, Y. Huang, Z. Cheng, X. Li, T. Sun, Y. Zhou and Z. Du: Downregulation of IncRNA-MALAT1 Affects Proliferation and the Expression of Stemness Markers in Glioma Stem Cell Line SHG139S. *Cell Mol Neurobiol* (2015) DOI: 10.1007/s10571-015-0303-6

- 104. J. Y. Liu, J. Yao, X. M. Li, Y. C. Song, X. Q. Wang, Y. J. Li, B. Yan and Q. Jiang: Pathogenic role of IncRNA-MALAT1 in endothelial cell dysfunction in diabetes mellitus. *Cell Death Dis*, 5, e1506 (2014) DOI: 10.1038/cddis.2014.466
- 105. A. E. Tee, B. Liu, R. Song, J. Li, E. Pasquier, B. B. Cheung, C. Jiang, G. M. Marshall, M. Haber, M. D. Norris, J. I. Fletcher, M. E. Dinger and T. Liu: The long noncoding RNA MALAT1 promotes tumor-driven angiogenesis by up-regulating pro-angiogenic gene expression. *Oncotarget*, 7(8), 8663-75 (2016) DOI: 10.18632/oncotarget.6675
- 106. K. M. Michalik, X. You, Y. Manavski, A. Doddaballapur, M. Zornig, T. Braun, D. John, Y. Ponomareva, W. Chen, S. Uchida, R. A. Boon and S. Dimmeler: Long noncoding RNA MALAT1 regulates endothelial cell function and vessel growth. *Circ Res*, 114(9), 1389-97 (2014)

DOI: 10.1161/CIRCRESAHA.114.303265

- 107. R. Lin, S. Maeda, C. Liu, M. Karin and T. S. Edgington: A large noncoding RNA is a marker for murine hepatocellular carcinomas and a spectrum of human carcinomas. *Oncogene*, 26(6), 851-8 (2007) DOI: 10.1038/sj.onc.1209846
- 108. M. Taniguchi, K. Fujiwara, Y. Nakai, T. Ozaki, N. Koshikawa, K. Toshio, M. Kataba, A. Oguni, H. Matsuda, Y. Yoshida, Y. Tokuhashi, N. Fukuda, T. Ueno, M. Soma and H. Nagase: Inhibition of malignant phenotypes of human osteosarcoma cells by a gene silencer, a pyrrole-imidazole polyamide, which targets an E-box motif. *FEBS Open Bio*, 4, 328-34 (2014)

DOI: 10.1016/j.fob.2014.03.004

109. F. Wang, S. Ren, R. Chen, J. Lu, X. Shi, Y. Zhu, W. Zhang, T. Jing, C. Zhang, J. Shen, C. Xu, H. Wang, H. Wang, Y. Wang, B. Liu, Y. Li, Z. Fang, F. Guo, M. Qiao, C. Wu, Q. Wei, D. Xu, D. Shen, X. Lu, X. Gao, J. Hou and Y. Sun: Development and prospective multicenter evaluation of the long noncoding RNA MALAT-1 as a diagnostic urinary biomarker for prostate cancer. *Oncotarget*, 5(22), 11091-102 (2014)

DOI: 10.18632/oncotarget.2691

- 110. M. H. Yang, Z. Y. Hu, C. Xu, L. Y. Xie, X. Y. Wang, S. Y. Chen and Z. G. Li: MALAT1 promotes colorectal cancer cell proliferation/ migration/invasion via PRKA kinase anchor protein 9. *Biochim Biophys Acta*, 1852(1), 166-74 (2015) DOI: 10.1016/j.bbadis.2014.11.013
- 111. X. Cao, R. Zhao, Q. Chen, Y. Zhao, B. Zhang, Y. Zhang, J. Yu, G. Han, W. Cao, J. Li and X. Chen: MALAT1 might be a predictive marker of poor prognosis in patients who underwent radical resection of middle thoracic esophageal squamous cell carcinoma. *Cancer Biomark*, 15(6), 717-23 (2015) DOI: 10.3233/cbm-150513
- 112. L. Hu, Y. Wu, D. Tan, H. Meng, K. Wang, Y. Bai and K. Yang: Up-regulation of long noncoding RNA MALAT1 contributes to proliferation and metastasis in esophageal squamous cell carcinoma. *J Exp Clin Cancer Res*, 34, 7 (2015)

DOI: 10.1186/s13046-015-0123-z

113. T. Gutschner, M. Hammerle, M. Eissmann, J. Hsu, Y. Kim, G. Hung, A. Revenko, G. Arun, M. Stentrup, M. Gross, M. Zornig, A. R. MacLeod, D. L. Spector and S. Diederichs: The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. *Cancer Res*, 73(3), 1180-9 (2013)

DOI: 10.1158/0008-5472.can-12-2850

- 114. A. Lane, L. M. Chuk, P. B. Colditz and A. Coulthard: The MRI-compatible neonatal incubator in practice. *J Paediatr Child Health*, 49(9), E377-80 (2013) DOI: 10.1.111/jpc.12222
- 115. L. M. Koontz, Y. Liu-Chittenden, F. Yin, Y. Zheng, J. Yu, B. Huang, Q. Chen, S. Wu and D. Pan: The Hippo effector Yorkie controls normal tissue growth by antagonizing scalloped-mediated default repression. *Dev Cell*, 25(4), 388-401 (2013) DOI: 10.1016/j.devcel.2013.04.021
- 116. S. Lv, G. Cheng, Y. Zhou and G. Xu: Thymosin beta4 induces angiogenesis through Notch signaling in endothelial cells. *Mol Cell Biochem*, 381(1-2), 283-90 (2013) DOI: 10.1007/s11010-013-1713-8
- 117. A. Lawniczek-Walczyk, R. L. Gorny,

M. Golofit-Szymczak, A. Niesler and A. Wlazlo: Occupational exposure to airborne microorganisms, endotoxins and beta-glucans in poultry houses at different stages of the production cycle. *Ann Agric Environ Med*, 20(2), 259-68 (2013)

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