New Insights into Long Non-Coding RNA MALAT1 in Cancer and Metastasis

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Abstract: Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is one of the most abundant, long non-coding RNAs (lncRNAs) in normal tissues. This lncRNA is highly conserved among mammalian species, and based on in vitro results, has been reported to regulate alternative pre-mRNA splicing and gene expression. However, Malat1 knockout mice develop and grow normally, and do not show alterations in alternative splicing. While MALAT1 was originally described as a prognostic marker of lung cancer metastasis, emerging evidence has linked this lncRNA to other cancers, such as breast cancer, prostate cancer, pancreatic cancer, glioma, and leukemia. The role described for MALAT1 is dependent on the cancer types and the experimental model systems. Notably, different or opposite phenotypes resulting from different strategies for inactivating MALAT1 have been observed, which led to distinct models for MALAT1’s functions and mechanisms of action in cancer and metastasis. In this review, we reflect on different experimental strategies used to study MALAT1’s functions, and discuss the current mechanistic models of this highly abundant and conserved lncRNA.

Keywords: lncRNA; MALAT1; metastasis

1. Introduction

Long non-coding RNAs (lncRNAs) are transcripts that are longer than 200 nucleotides (nt) without protein-coding capacity. Despite the exponential growth in lncRNA publications, our understanding of lncRNA functions and mechanisms is still limited, and outstanding caveats and controversies remain in the current lncRNA knowledge [1,2]. The mechanisms of action of some well-known lncRNAs are currently under discussion [3–11]. Questions have also been raised as to whether phenotypes arising from deleting or inactivating a lncRNA gene can be unequivocally attributed to the loss of the lncRNA per se [1]. A recent study revealed opposite effects from the deletion and insertional inactivation of the lncRNA-encoding gene Haunt, and remarkably, the gene deletion effect was due to the loss of Haunt genomic DNA, which dominated the effect of Haunt lncRNA loss [12]. In light of the accumulating evidence for different or opposite phenotypes resulting from different strategies for inactivating the same lncRNA (e.g., Fendrr, Ecf2, and lincRNA-p21) in vivo, it has been concluded that genetic rescue experiments, where the lncRNA is re-expressed from an independent transgene, are essential for separating RNA-specific effects from those resulting from the manipulation of the genomic DNA [1]; however, such rescue experiments are generally lacking in the current lncRNA research, especially in cancer studies, making it difficult to interpret many lncRNA results in the cancer field.

Unlike messenger RNAs (mRNAs) and microRNAs (miRNAs), many lncRNAs have poor evolutionary conservation; however, a nuclear lncRNA, metastasis-associated lung adenocarcinoma
transcript 1 (MALAT1, also known as nuclear enriched abundant transcript 2, NEAT2), is exceptionally conserved for lncRNA, and is among the most abundantly expressed lncRNAs in normal tissues [13]. Despite its length (~8 kb in humans and ~7 kb in mice), MALAT1 is a single-exon gene whose transcript is subject to further processing; for instance, in mice, Malat1 gives rise to a 7 kb full-length transcript (low expression, nuclear), a 6.7 kb lncRNA (high expression, nuclear), and a 61 nt tRNA-like small RNA (mascRNA, exported to the cytoplasm with unknown functions) [14]. At the molecular level, MALAT1 lncRNA is recruited to nuclear speckles and has been reported to regulate pre-mRNA splicing [13,15]. However, this finding is not supported by Malat1 knockout mice, which showed normal development and growth and no global difference in alternative splicing [16–18]. In addition, MALAT1 lncRNA is subject to post-transcriptional modifications, such as N6-methyladenosine (m6A) [19] and 5-methylcytosine (m5C) [20], but the functional consequences of these modifications remain unknown.

Originally, MALAT1 was identified as a prognostic marker for poor clinical outcomes (overall survival and metastasis-free survival outcomes) in patients with early-stage non-small cell lung cancer [21]. To date, there are more than 800 publications related to MALAT1 (the PubMed search word “MALAT1” generated 809 results as of 13 February, 2019) and many of them reported a role of MALAT1 in cancer, making MALAT1 one of the most studied lncRNAs. Intriguingly, different studies yielded conflicting results about MALAT1’s functions and mechanisms of action. In this review, we discuss the progress and controversies in MALAT1 research, and reflect on the approaches and experimental design used for lncRNA studies.

2. Does MALAT1 Regulate Alternative pre-mRNA Splicing and Global Gene Expression?

By performing RNA fluorescent in situ hybridization and protein immunofluorescent staining, Hutchinson et al. found that MALAT1 lncRNA co-localizes with SC35 nuclear speckles, structures involved in pre-mRNA processing [13]. Subsequently, based on small interfering RNA (siRNA) knockdown results from cultured cell lines, MALAT1 was identified as a nuclear-retained regulatory RNA that interacts with the serine/arginine-rich family of splicing factors, affects the distribution of splicing factors in nuclear speckle domains, and regulates alternative splicing of pre-mRNAs [15]. Moreover, by using the CHART-seq technology, West et al. identified hundreds of MALAT1-binding sites in human cells and most of these sites are on actively transcribed genes, indicating that MALAT1 might be involved in regulating gene transcription [22]. However, these effects were absent in genetically engineered mouse models lacking Malat1 expression [16–18].

In 2012, three Malat1 knockout mouse models, generated by different strategies, were reported by independent groups. Zhang et al. removed a 3 kb genomic region encompassing the 5’ end of Malat1 and its promoter (Figure 1a) [16]. Eissmann et al. deleted the entire 7 kb mouse Malat1 gene (Figure 1b) [17]. Nakagawa et al. disrupted the Malat1 gene by inserting a transcriptional terminator (lacZ and the polyadenylation sequences) 69 bp downstream of the transcriptional start site of Malat1 (Figure 1c); similar to the two gene deletion strategies, this insertional inactivation approach also abrogated Malat1 RNA expression in mice, as gauged by Northern blot analysis and in situ hybridization [18]. Surprisingly, none of these three models showed phenotypes, and loss of Malat1 in mice did not affect global gene expression, nuclear speckles, or alternative pre-mRNA splicing [16–18], which argues against the in vitro siRNA knockdown results [13,15,22]. This discrepancy suggests that in vitro findings could be cell line-specific, or rely on specific experimental settings and approaches. Alternatively, Malat1 may have stress-dependent functions in vivo. It is also possible that additional factors compensate for the effects of Malat1 loss in mice. These possibilities warrant further investigation.
However, unlike genetic deletion, ASO treatment significantly decreased the tumor volume (by ~50%), suggesting that these ASOs have extra effects. In addition, after treating MMTV-PyMT mice with antisense oligonucleotides (ASOs), Arun et al. also observed increased cystic areas in primary tumors and decreased lung metastases [42]. Notably, despite no metastasis reduction observed in this model. In contrast, other studies reported that MALAT1 promotes cell proliferation, migration, tumor growth, metastasis, and chemoresistance [31–37]. In contrast, other studies reported that MALAT1 inhibits cell proliferation, tumor growth, invasion, and epithelial-mesenchymal transition (EMT) [27,28,30–32].

As mentioned above, one of the three Malat1 knockout mouse models harbors a 3 kb deletion of Malat1’s promoter and its 5′ end [16]. After breeding these mice to a metastasis-prone transgenic model of breast cancer, MMTV (mouse mammary tumor virus)-PyMT (polyomavirus middle T antigen) mice [41], Arun et al. observed a reduction of lung metastases [42]. Notably, despite no difference in mammary tumor size, Malat1 gene-deleted PyMT tumors were liquid-filled and much more differentiated with a drastically increased cystic phenotype [42], which might underlie the metastasis reduction observed in this model. In addition, after treating MMTV-PyMT mice with Malat1 antisense oligonucleotides (ASOs), Arun et al. also observed increased cystic areas in primary tumors and decreased lung metastases [42]. However, unlike genetic deletion, ASO treatment significantly...
decreased the tumor volume (by ~50%), suggesting that these ASOs have extra effects other than knocking down Malat1. Unfortunately, the molecular mechanisms underlying the Malat1 gene deletion and ASO effects remain unknown.

In stark contrast, after mice with targeted insertional inactivation of Malat1 [18] were bred to MMTV-PyMT mice of a C57BL/6 strain, our group found that the transcriptional inactivation of Malat1 induced a striking increase in the number of visible metastatic nodules and in the number and area of metastatic foci in the lungs [29]. Importantly, the metastatic-promoting effect of Malat1 insertional inactivation, which contradicted the Malat1 genomic deletion effect, was completely reversed by the genetic add-back of Malat1 achieved via breeding to mice with targeted transgenic expression of Malat1 from the ROSA26 locus [29]. Consistently, after MMTV-PyMT mice on an FVB background were crossed to the Malat1 transgenic mice on an FVB background, overexpression of Malat1 markedly suppressed lung metastasis [29]. In contrast to the gene deletion model [42], our group found that Malat1 wild-type, Malat1-inactivated, and Malat1-overexpressing PyMT tumors showed similar degrees of cystic areas and high-grade carcinoma areas [29]. Interestingly, insertional disruption of Malat1 significantly elevated the percentages of circulating tumor cells (CTCs) in the peripheral blood of MMTV-PyMT mice, which was also reversed by restoration of Malat1 expression. Furthermore, CRISPR (clustered regularly interspaced short palindromic repeats)-Cas9-mediated knockout of MALAT1 (~650 bp deletion of the 5' end) in the MDA-MB-231 breast cancer cell line promoted cell migration and invasion in vitro and lung metastasis in vivo, which could be reversed by ectopic expression of mouse Malat1. Conversely, overexpression of Malat1 in LM2 human breast cancer cells and in 4T1 mouse mammary tumor cells led to a pronounced reduction of their lung metastatic ability in experimental metastasis assays [29]. Taken together, targeted inactivation, restoration (genetic rescue), and overexpression of MALAT1 in multiple in vivo models suggest that the lncRNA MALAT1 suppresses breast cancer metastasis.

4. Experimental Dissection of MALAT1 and Other lncRNAs

What led to inconsistent conclusions about MALAT1’s function? While it remains to be determined whether this is dependent on different cell/tissue types, cancer types, and genetic backgrounds, we can carefully examine the experimental settings and approaches that have been used to study MALAT1 and other lncRNAs; this offers important lessons. In fact, substantially different or opposite phenotypes arising from different strategies (e.g., gene deletion, insertional inactivation, CRISPR-Cas9, and RNAi) for inactivating the same lncRNA are not uncommon.

In mice, genetic deletion of the lncRNA Fendrr resulted in lung and gastrointestinal tract defects [43], whereas transcriptional terminator insertion led to heart and body wall defects [44]; the defects caused by insertional inactivation were rescued by a Fendrr transgene [44]. Moreover, RNAi experiments showed that the lncRNA Eoz2 is important for activating Dlx5/6 expression [45], but transcriptional terminator insertion in mice caused the opposite effect on Dlx5/6 expression [46]; the effect caused by insertional inactivation could be rescued by Eoz2 expression from a separate transgene [47]. Strikingly, a recent study reported opposing effects from the lncRNA Haunt gene deletion and insertional inactivation [12]. The Haunt genomic locus contains enhancers for HOXA genes, while Haunt lncRNA inhibits HOXA expression by binding to chromatin [12]. Yin et al. showed that CRISPR-Cas9-mediated large deletion of the Haunt genomic locus attenuated HOXA gene activation during retinoic acid-induced embryonic stem cell differentiation, whereas minimal disruption of genomic sequences, such as insertional inactivation by CRISPR knockin, abrogated Haunt transcription and upregulated HOXA expression [12]. Notably, Haunt cDNA was unable to “rescue” the deletion phenotype [12], suggesting that the Haunt genomic deletion effect dominated the effect of Haunt lncRNA loss. These and other studies strongly demonstrate the importance of rescue experiments.

Two excellent reviews discussed considerations when investigating lncRNAs in general [1,2]. The vast majority of MALAT1 reports are based on siRNA or short-hairpin RNA (shRNA) experiments, and a few studies [42,48,49] used ASOs. However, nuclear RNAi is not fully established and the RNAi
approach can be problematic for nuclear RNAs. Silencing a nuclear RNA by siRNA or shRNA requires nuclear Ago2 and other RNAi factors [50]. It has been shown that subcellular localization of Ago2 depends on cell/tissue types and genetic backgrounds [51].

If a cell line or tissue does not have nuclear Ago2, the specificity of the MALAT1 siRNA or shRNA should be questioned. It should be noted that antisense RNAs can have substantial non-specific effects, and that an alarming and growing number of claimed anticancer targets have been invalidated due to recent proof for off-target effects of previously used antisense RNAs and chemical inhibitors [52]. For example, MELK was previously identified as a kinase required for tumor cell survival and proliferation in several cancer types. RNAi and small-molecule inhibitors of MELK demonstrated anticancer efficacies in many studies, and one of the MELK inhibitors, OTS167, entered several clinical trials. Recently, however, multiple studies [53–56] demonstrated that these results were caused by off-target effects, thereby invalidating MELK as an anticancer target reported by many groups. For these reasons, it is crucial to rule out off-target effects of antisense RNAs by genetic add-back of RNAi-resistant mutants and by multiple loss-of-function approaches. Unfortunately, so far no publication has demonstrated the specificity of the MALAT1 siRNA, shRNA, or ASO by rescue experiments or by MALAT1 knockout cells.

Previous cell culture and xenograft studies showed contradictory effects of MALAT1 on cancer cell growth, proliferation, and invasion [27,30–32,38–40]. With regard to genetically engineered mouse models, opposite phenotypes were also observed. Whereas genetic deletion of Malat1 in MMTV-PyMT mice inhibited lung metastasis [42], our group found that targeted insertional inactivation of Malat1 promoted lung metastasis in the PyMT mouse model [29]. It should be noted that we were able to reverse the insertional inactivation phenotype by genetic add-back of Malat1 using a targeted Malat1 transgenic model [29], which suggests that the metastasis-promoting effect of Malat1 inactivation was due to the loss of Malat1 IncRNA.

Why did the two different Malat1 knockout mouse models show different phenotypes? As mentioned above, the Haunt IncRNA gene deletion effect has been attributed to the loss of the Haunt genomic DNA, which dominated the effect of Haunt RNA loss [12]. It is possible that the similar scenario applies to the Malat1 genomic locus versus Malat1 IncRNA, although the experimental evidence for this hypothesis is lacking at present. Notably, the Malat1 genomic deletion model showed significant upregulation of Malat1’s 12 adjacent genes [42]; in contrast, the Malat1 insertional inactivation model showed no changes in expression levels of these neighboring genes both in normal tissues and in mammary tumors [29]. It remains to be determined whether this is the reason for the different phenotypes of the two Malat1 knockout mouse models. Among the concerns about deletion of IncRNA genomic loci is that large deletions may eliminate regulatory elements for other genes or destroy long-range genomic interactions.

As mentioned above, the Malat1 gene generates several transcripts with different expression levels and localizations. It should be noted that all three different strategies used to generate Malat1 knockout mice eliminated all Malat1 transcripts including the uncharacterized transcripts, and that our group used full-length Malat1 to restore its expression in Malat1-deficient mice and in MALAT1-knockout human cells. Among the transcripts derived from the Malat1 gene locus, the nuclear IncRNA Malat1 is the predominant form and is expected to be the functional form. Nevertheless, functional dissection of different transcripts warrants future studies.

5. Mechanistic Models of MALAT1 in Cancer and Metastasis

LncRNAs function through binding to other RNA, genomic DNA, or protein. Specifically, a lncRNA can serve as a scaffold that keeps proteins together, as a guide that helps recruit proteins to specific genomic DNA sequences, or as a molecular decoy (also called “sponge”) for proteins and other RNAs. In this section, we discuss several molecular mechanisms by which MALAT1 regulates tumor progression and metastasis.
5.1. MALAT1 Serves a Competitive Endogenous RNA (ceRNA)

MALAT1 is a long and highly abundant lncRNA that contains many putative binding sites of miRNAs. A number of studies reported that MALAT1 functions through sponging miRNAs, including miR-145 [57], miR-1 [58], miR-202 [59], miR-200c [60], miR-206 [61], and so on. In these studies, the authors typically showed that siRNA-mediated knockdown of MALAT1 in cancer cell lines resulted in a certain phenotype, such as proliferation, migration, invasion, chemosensitivity, or radiosensitivity, followed by luciferase assays to demonstrate the existence of the miRNA-binding site on MALAT1. Then, functional experiments demonstrated that the miRNA and its target gene mediate the effect of MALAT1. While the ceRNA model is interesting and MALAT1 might function as a ceRNA under certain circumstances, more rigorous experiments are needed to prove this model. For instance, the specificity of the siRNAs targeting MALAT1 or the miRNA targets should be clearly addressed. Moreover, it would be critical to demonstrate that the miRNA-binding site on MALAT1 is important for its function—key evidence that is generally lacking. In addition, gain-of-function experiments would further strengthen the conclusions. Furthermore, if MALAT1 functions through sponging multiple miRNAs, it is very challenging to experimentally prove the ceRNA model of MALAT1 (Figure 2a).

![Figure 2. Mechanistic models of MALAT1 in cancer and metastasis. (a) MALAT1 sponges miRNAs, leading to repression of miRNA target mRNAs. (b) MALAT1 binds PRC2 components and recruits PRC2 to target gene loci. (c) MALAT1 binds, sequesters, and inactivates TEAD.](image)

5.2. MALAT1 Interacts with the PRC2 Complex

Polycomb repressive complex 2 (PRC2) catalyzes histone H3K27 methylation, which plays important roles in transcriptional repression and cancer [63]. HOTAIR was the first reported PRC2-binding lncRNA that recruits PRC2 to target gene loci [64]. Subsequently, it has been shown that HOTAIR directly interacts with EZH2 [65], and that HOTAIR negatively regulates epithelial gene expression through H3K27 trimethylation [66,67]. Recently, additional lncRNAs, including MALAT1, have been shown to bind PRC2 components (Figure 2b). Fan et al. reported that MALAT1 binds SUZ12, a subunit of the PRC2 complex, and that MALAT1 and SUZ12 mediate TGF-β-induced EMT in bladder cancer [68]. Hirata et al. showed that MALAT1 interacts with EZH2, the catalytic subunit of PRC2, and that both MALAT1 and EZH2 are required for the EMT in renal cell carcinoma [69]. In addition, several studies showed that the interaction of MALAT1 with EZH2 is involved in other cancer types, such as prostate cancer [70], gastric cancer [71], and lymphoma [72]. However, it remains unclear whether and how the MALAT1-PRC2 interaction specifically regulates the transcription of target genes. Notably, a recent EZH2 RIP-seq assay identified more than 1,000 EZH2-binding lncRNAs [73], while it is unclear whether and how these lncRNAs regulate the activity of EZH2. Similarly, studies from Cech and
colleagues revealed promiscuous RNA binding by PRC2 and indicated that mammalian PRC2 binds thousands of RNAs in vivo [74,75]. While the hypothesis that IncRNAs recruit chromatin-modifying complexes to target gene loci is intriguing, questions remain regarding the molecular mechanism by which IncRNAs regulate transcription.

5.3. MALAT1 Binds and Inactivates TEAD

Recently, our group performed a chromatin isolation by RNA purification coupled to mass spectrometry (ChIRP-MS) assay to identify Malat1’s endogenous binding proteins in mammary tumors from MMTV-PyMT mice. We identified a list of 23 proteins that specifically bind to Malat1 but not two negative controls (nuclear RNA U1 and probe-free beads) [29]. Interestingly, all four members of the Tead transcription factor family (Tead1, Tead2, Tead3, and Tead4) were present in this list. Through subsequent validation by ChIRP-Western, RNA pulldown, RIP-qPCR, and UV crosslinking-immunoprecipitation and qPCR (CLIP-qPCR) assays, we found that MALAT1 binds to the transactivation domain of TEAD proteins, which are unconventional RNA-binding proteins (RBPs), but does not bind to GAPDH, histone H3, or the TEAD co-activator YAP [29]. Moreover, the results from TEAD reporter assays, co-IP, qPCR, ChIP-qPCR, and functional rescue experiments demonstrated that MALAT1 lncRNA sequesters the transcription factor TEAD, thereby blocking TEAD from associating with its co-activator YAP and target genes, which in turn leads to inhibition of TEAD’s transcriptional activity and pro-metastatic function in breast cancer [29] (Figure 2c). It remains to be determined whether MALAT1 suppresses metastasis by inactivating TEAD in other cancer types. In addition, the functional consequences of the interaction of Malat1 with its other binding partners warrant further studies.

5.4. MALAT1 Regulates Multiple Signaling Pathways

In addition to the Hippo-YAP pathway, MALAT1 has been reported to regulate other signaling pathways in cancer, including PI3K-AKT, MAPK, WNT, and NF-κB pathways. For instance, by modulating Wnt signaling, MALAT1 has been shown to regulate cancer cell EMT, migration, invasion, and metastasis [76–78]. MALAT1 was also found to regulate hepatocellular carcinoma progression through the mTOR pathway [79]. In certain cancer types, a MALAT1–NF-κB axis is involved in chemoresistance and EMT [80,81], and PI3K-AKT signaling has been found to mediate the effect of MALAT1 on metastasis [30,82,83]. Moreover, MALAT1 may regulate proliferation and metastasis of esophageal squamous cell carcinoma through the ATM-CHK2 pathway [84]. In addition, MALAT1 has been reported to regulate tumor cell proliferation through the MAPK pathway [27,36]. Unfortunately, validation of these results in genetically engineered mouse models is lacking, and very little is known about the molecular mechanisms by which MALAT1 regulates these pathways.

6. Conclusions and Future Perspectives

As one of the most abundantly expressed lncRNAs in normal tissues, MALAT1 has attracted substantial interests from multiple fields including the cancer field. Malat1 knockout mice are viable and develop normally, suggesting that MALAT1 is dispensable for development. It remains to be determined whether this lncRNA plays important roles in stress responses or various pathological processes, such as cardiac stress, vascular injury, intestinal injury, immune response, and various oncogenic insults, and whether mice with Malat1 deficiency show phenotypes in response to external or internal perturbations.

MALAT1 was previously described by many papers as a cancer-promoting and metastasis-promoting lncRNA, while other reports suggested a tumor-suppressing role of MALAT1. A major pitfall in these studies was the lack of rescue experiments for loss-of-function approaches. In contrast, our group conducted genetic rescue experiments to demonstrate that the metastasis induction by Malat1 germline inactivation or somatic knockout (CRISPR-Cas9) was specific to the loss of MALAT1 lncRNA [29]. This finding underscores the importance of rigorous
characterization of IncRNAs, and illustrates how a lncRNA can interact with unconventional RBPs (TEAD proteins) to inhibit metastasis. Non-coding RNA functions should be unambiguously established by rescue experiments in which the RNA expression is restored in knockout cells or knockout mice by means of an independent transgene. Moreover, it is critical to rule out non-specific effects in all types of loss-of-function experiments, including gene deletion, insertional inactivation, CRISPR-Cas9, RNAi, ASO, and chemical inhibition; this is particularly important for the validation of anticancer targets. The current understanding of IncRNAs remains very limited. Moreover, RNA modifications and RBPs can regulate RNA’s fate; on the other hand, RBPs, especially unconventional RBPs, could be controlled by RNA, as exemplified by the MALAT1-TEAD interaction [29]. We still have a lot to learn about lncRNAs and a lot to expect from the discovery of RNA epigenetics and many new unconventional RBPs. The ongoing and future studies will profoundly advance understanding of the roles of RNA biology in tumor progression and metastasis, and will likely unearth novel anti-metastatic targets for treatment.

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References
1. Bassett, A.R.; Akhtar, A.; Barlow, D.P.; Bird, A.P.; Brockdorff, N.; Duboule, D.; Ephrussi, A.; Ferguson-Smith, A.C.; Gingeras, T.R.; Haerty, W.; et al. Considerations when investigating lncRNA function in vivo. Elife 2014, 3, e03058. [CrossRef]
2. Kopp, F.; Mendell, J.T. Functional Classification and Experimental Dissection of Long Noncoding RNAs. Cell 2018, 172, 393–407. [CrossRef]
3. Zhao, J.; Sun, B.K.; Erwin, J.A.; Song, J.J.; Lee, J.T. Polycomb proteins targeted by a short repeat RNA to the mouse X chromosome. Science 2008, 322, 750–756. [CrossRef]
4. Chen, C.K.; Blanco, M.; Jackson, C.; Aznaruyan, E.; Ollikainen, N.; Surka, C.; Chow, A.; Cerse, A.; McDonel, P.; Guttman, M. Xist recruits the X chromosome to the nuclear lamina to enable chromosome-wide silencing. Science 2016, 354, 468–472. [CrossRef]
5. Wang, C.Y.; Froberg, J.E.; Blum, R.; Jeon, Y.; Lee, J.T. Comment on “Xist recruits the X chromosome to the nuclear lamina to enable chromosome-wide silencing”. Science 2017, 356. [CrossRef]
6. Chen, C.K.; Chow, A.; Lai, M.; Guttman, M. Response to Comment on “Xist recruits the X chromosome to the nuclear lamina to enable chromosome-wide silencing”. Science 2017, 356. [CrossRef]
7. Rinn, J.L.; Kertesz, M.; Wang, J.K.; Squazzo, S.L.; Xu, X.; Brugmann, S.A.; Goodnough, L.H.; Helms, J.A.; Farnham, P.J.; Segal, E.; et al. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell 2007, 129, 1311–1323. [CrossRef]
8. Li, L.; Liu, B.; Wapinski, O.L.; Tsai, M.C.; Qu, K.; Zhang, J.; Carlson, J.C.; Lin, M.; Fang, F.; Gupta, R.A.; et al. Targeted disruption of Hotair leads to homeotic transformation and gene derepression. Cell Rep. 2013, 5, 3–12. [CrossRef]
9. Amandio, A.R.; Necsulea, A.; Joye, E.; Mascrecz, B.; Duboule, D. Hotair Is Dispensable for Mouse Development. PLoS Genet. 2016, 12, e1006232. [CrossRef]
10. Li, L.; Helms, J.A.; Chang, H.Y. Comment on “Hotair Is Dispensable for Mouse Development”. PLoS Genet. 2016, 12, e1006406. [CrossRef]
11. Selleri, L.; Bartolomei, M.S.; Bickmore, W.A.; He, L.; Stubbs, L.; Reik, W.; Barsh, G.S. A Hox-Embedded Long Noncoding RNA: Is It All Hot Air? PLoS Genet. 2016, 12, e1006485. [CrossRef] [PubMed]
12. Yin, Y.; Yan, P.; Lu, J.; Song, G.; Zhu, Y.; Li, Z.; Zhao, Y.; Shen, B.; Huang, X.; Zhu, H.; et al. Opposing Roles for the IncRNA Haunt and Its Genomic Host in Regulating HOXA Gene Activation during Embryonic Stem Cell Differentiation. *Cell Stem Cell* 2015, 16, 504–516. [CrossRef] [PubMed]

13. Hutchinson, J.N.; Ensminger, A.W.; Clemson, C.M.; Lynch, C.R.; Lawrence, J.B.; Chess, A. A screen for nuclear transcripts identifies two linked noncoding RNAs associated with SC35 splicing domains. *BMC Genomics* 2007, 8, 39. [CrossRef] [PubMed]

14. Wilusz, J.E.; Freier, S.M.; Spector, D.L. 3' end processing of a long nuclear-retained noncoding RNA yields a tRNA-like cytoplasmic RNA. *Cell* 2008, 135, 919–932. [CrossRef] [PubMed]

15. Tripathi, V.; Ellis, J.D.; Shen, Z.; Song, D.Y.; Pan, Q.; Watt, A.T.; Freier, S.M.; Bennett, C.F.; Sharma, A.; Bubulya, P.A.; et al. The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. *Mol. Cell* 2010, 39, 925–938. [CrossRef]

16. Zhang, B.; Arun, G.; Mao, Y.S.; Lazar, Z.; Hung, G.; Bhattacharjee, G.; Xiao, X.; Booth, C.J.; Wu, J.; Zhang, C.; et al. The IncRNA Malat1 is dispensable for mouse development but its transcription plays a cis-regulatory role in the adult. *Cell Rep.* 2012, 1, 111–123. [CrossRef]

17. Eissmann, M.; Gutschner, T.; Hammerle, M.; Gunther, S.; Caudron-Herger, M.; Gross, M.; Schirmacher, P.; Rippe, K.; Braun, T.; Zornig, M.; et al. Loss of the abundant nuclear non-coding RNA MALAT1 is compatible with life and development. *RNA Biol.* 2012, 9, 1076–1087. [CrossRef]

18. Nakagawa, S.; Ip, J.Y.; Shioi, G.; Tripathi, V.; Zong, X.; Hirose, T.; Prasanth, K.V. Malat1 is not an essential component of nuclear speckles in mice. *RNA* 2012, 18, 1487–1499. [CrossRef]

19. Liu, N.; Zhou, K.I.; Parisien, M.; Dai, Q.; Diatchenko, L.; Pan, T. N6-methyladenosine alters RNA structure to regulate binding of a low-complexity protein. *Nucleic Acids Res.* 2017, 45, 6051–6063. [CrossRef]

20. Amort, T.; Rieder, D.; Wille, A.; Khokhlova-Cubberley, D.; Riml, C.; Trixl, L.; Jia, X.Y.; Micura, R.; Lusser, A. Distinct 5-methylcytosine profiles in poly(A) RNA from mouse embryonic stem cells and brain. *Genome Biol.* 2017, 18, 1. [CrossRef]

21. Ji, P.; Diederichs, S.; Wang, W.; Boing, S.; Metzger, R.; Schneider, P.M.; Tidow, N.; Brandt, B.; Buerger, H.; Bulk, E.; et al. MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene* 2003, 22, 8031–8041. [CrossRef]

22. West, J.A.; Davis, C.P.; Sunwoo, H.; Simon, M.D.; Sadreyev, R.I.; Wang, P.I.; Tolstorukov, M.Y.; Kingston, R.E. The long noncoding RNAs NEAT1 and MALAT1 bind active chromatin sites. *Mol. Cell* 2014, 55, 791–802. [CrossRef]

23. Gutschner, T.; Hammerle, M.; Diederichs, S. MALAT1—a paradigm for long noncoding RNA function in cancer. *J. Mol. Med. (Berl.)* 2013, 91, 791–801. [CrossRef]

24. Yoshimoto, R.; Mayeda, A.; Yoshida, M.; Nakagawa, S. MALAT1 long non-coding RNA in cancer. *Biochim. Biophys. Acta* 2016, 1859, 192–199. [CrossRef]

25. Liu, J.; Peng, W.X.; Mo, Y.Y.; Luo, D. MALAT1-mediated tumorigenesis. *Front. Biosci. (Landmark Ed.)* 2017, 22, 66–80.

26. Zhao, M.; Wang, S.; Li, Q.; Ji, Q.; Guo, P.; Liu, X. MALAT1: A long non-coding RNA highly associated with human cancers. *OncoLett.* 2018, 16, 19–26. [CrossRef]

27. Han, Y.; Wu, Z.; Wu, T.; Huang, Y.; Cheng, Z.; Li, X.; Sun, T.; Xie, X.; Zhou, Y.; Du, Z. Tumor-suppressive function of long noncoding RNA MALAT1 in glioma cells by downregulation of MMP2 and inactivation of ERK/MAPK signaling. *Cell Death Dis.* 2016, 7, e2123. [CrossRef]

28. Kwok, Z.H.; Roche, V.; Chew, X.H.; Fadiseieva, A.; Tay, Y. A non-canonical tumor suppressor role for the long non-coding RNA MALAT1 in colon and breast cancers. *Int. J. Cancer* 2018, 143, 668–678. [CrossRef]

29. Kim, J.; Piao, H.L.; Kim, B.J.; Yao, F.; Han, Z.; Wang, Y.; Xiao, Z.; Siverly, A.N.; Lawhon, S.E.; Ton, B.N.; et al. Long noncoding RNA MALAT1 suppresses breast cancer metastasis. *Nat. Genet.* 2018, 50, 1705–1715. [CrossRef]

30. Xu, S.; Sui, S.; Zhang, J.; Bai, N.; Shi, Q.; Zhang, G.; Gao, S.; You, Z.; Zhan, C.; Liu, F.; et al. Downregulation of long noncoding RNA MALAT1 induces epithelial-to-mesenchymal transition via the PI3K-AKT pathway in breast cancer. *Int. J. Clin. Exp. Pathol.* 2015, 8, 4881–4891.
32. Ji, Q.; Zhang, L.; Liu, X.; Zhou, L.; Wang, W.; Han, Z.; Sui, H.; Tang, Y.; Wang, Y.; Liu, N.; et al. Long non-coding RNA MALAT1 promotes tumour growth and metastasis in colorectal cancer through binding to SFPQ and releasing oncogene PTBP2 from SFPQ/PTBP2 complex. *Br. J. Cancer* **2014**, *111*, 736–748. [CrossRef] [PubMed]

33. Bi, S.; Wang, C.; Li, Y.; Zhang, W.; Zhang, J.; Lv, Z.; Wang, J. LncRNA-MALAT1-mediated Axl promotes cell invasion and migration in human neuroblastoma. *Tumour Biol.* **2017**, *39*, 1010428317699796. [CrossRef] [PubMed]

34. Li, P.; Zhang, X.; Wang, H.; Wang, L.; Liu, T.; Du, L.; Yang, Y.; Wang, C. MALAT1 Is Associated with Poor Response to Oxaliplatin-Based Chemotherapy in Colorectal Cancer Patients and Promotes Chemoresistance through EZH2. *Mol. Cancer Ther.* **2017**, *16*, 739–751. [CrossRef]

35. Tripathi, V.; Shen, Z.; Chakraborty, A.; Giri, S.; Freier, S.M.; Wu, X.; Gorospe, M.; Prasanth, S.G.; Lal, A.; et al. Long noncoding RNA MALAT1 controls cell cycle progression by regulating the expression of oncogenic transcription factor B-MYB. *PLoS Genet.* **2013**, *9*, e1003368. [CrossRef]

36. Wu, X.S.; Wang, X.A.; Wu, W.G.; Hu, Y.P.; Li, M.L.; Ding, Q.; Weng, H.; Shu, Y.J.; Liu, T.Y.; Jiang, L.; et al. MALAT1 promotes the proliferation and metastasis of gallbladder cancer cells by activating the ERK/MAPK pathway. *Cancer Biol. Ther.* **2014**, *15*, 806–814. [CrossRef] [PubMed]

37. Shen, L.; Chen, L.; Wang, Y.; Jiang, X.; Xia, H.; Zhuang, Z. Long noncoding RNA MALAT1 promotes brain metastasis by inducing epithelial-mesenchymal transition in lung cancer. *J. Neurooncol.* **2015**, *121*, 101–108. [CrossRef] [PubMed]

38. Cao, S.; Wang, Y.; Li, J.; Lv, M.; Niu, H.; Tian, Y. Tumor-suppressive function of long noncoding RNA MALAT1 in glioma cells by suppressing miR-155 expression and activating FBXW7 function. *Am. J. Cancer Res.* **2016**, *6*, 2561–2574. [PubMed]

39. Han, Y.; Zhou, L.; Wu, T.; Huang, Y.; Cheng, Z.; Li, X.; Sun, T.; Zhou, Y.; Du, Z. Downregulation of lncRNA-MALAT1 Affects Proliferation and the Expression of Stemness Markers in Glioma Stem Cell Line SHG139S. *Cell. Mol. Neurobiol.* **2016**, *36*, 1097–1107. [CrossRef]

40. Latorre, E.; Carelli, S.; Raimondi, I.; D’Agostino, V.; Castiglioni, I.; Zucal, C.; Moro, G.; Luciani, A.; Ghilardi, G.; Monti, E.; et al. The Ribonucleic Complex HuR-MALAT1 Represses CD133 Expression and Suppresses Epithelial-Mesenchymal Transition in Breast Cancer. *Cancer Res.* **2016**, *76*, 2626–2636. [CrossRef]

41. Guy, C.T.; Cardiff, R.D.; Muller, W.J. Induction of mammary tumors by expression of polyomavirus middle T oncogene: A transgenic mouse model for metastatic disease. *Mol. Cell. Biol.* **1992**, *12*, 954–961. [CrossRef]

42. Arun, G.; Diermeier, S.; Akerman, M.; Chang, K.C.; Wilkinson, J.E.; Hearn, S.; Kim, Y.; MacLeod, A.R.; Kainer, A.R.; Norton, L.; et al. Differentiation of mammary tumors and reduction in metastasis upon Malat1 lncRNA loss. *Genes Dev.* **2016**, *30*, 34–51. [CrossRef]

43. Sauvageau, M.; Goff, L.A.; Lodato, S.; Bonev, B.; Groff, A.F.; Gerhardinger, C.; Sanchez-Gomez, D.B.; Hacisuleyman, E.; Li, E.; Spence, M.; et al. Multiple knockout mouse models reveal lincRNAs are required for life and brain development. *Elife* **2013**, *2*, e01749. [CrossRef] [PubMed]

44. Grote, P.; Wittler, L.; Hendrix, D.; Koch, F.; Wahrisch, S.; Beisaw, A.; Macura, K.; Blass, G.; Kellis, M.; Werber, M.; et al. The tissue-specific lncRNA Fendrr is an essential regulator of heart and body wall development in the mouse. *Dev. Cell* **2013**, *24*, 206–214. [CrossRef]

45. Feng, J.; Bi, C.; Clark, B.S.; Mady, R.; Shah, P.; Kohtz, J.D. The Evf-2 noncoding RNA is transcribed from the Dlx-5/6 ultraconserved region and functions as a Dlx-2 transcriptional coactivator. *Genes Dev.* **2006**, *20*, 1470–1484. [CrossRef] [PubMed]

46. Bond, A.M.; Vangompel, M.J.; Sametsky, E.A.; Clark, M.F.; Savage, J.C.; Disterhoft, J.F.; Kohtz, J.D. Balanced gene regulation by an embryonic brain ncRNA is critical for adult hippocampal GABA circuitry. *Nat. Neurosci.* **2009**, *12*, 1020–1027. [CrossRef] [PubMed]

47. Berghoff, E.G.; Clark, M.F.; Chen, S.; Cajigas, I.; Leib, D.E.; Kohtz, J.D. Evf2 (Dlx6as) lncRNA regulates ultraconserved enhancer methylation and the differential transcriptional control of adjacent genes. *Development* **2013**, *140*, 4407–4416. [CrossRef] [PubMed]

48. Gutschner, T.; Hammerle, M.; Eissmann, M.; Hsu, J.; Kim, Y.; Hung, G.; Revenko, A.; Arun, G.; Stentrup, M.; Gross, M.; et al. The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. *Cancer Res.* **2013**, *73*, 1180–1189. [CrossRef] [PubMed]
49. Jadaliha, M.; Zong, X.; Malakar, P.; Ray, T.; Singh, D.K.; Freier, S.M.; Jensen, T.; Prasanth, S.G.; Karni, R.; Ray, P.S.; et al. Functional and prognostic significance of long non-coding RNA MALAT1 as a metastasis driver in ER negative lymph node negative breast cancer. *Oncotarget* 2016, 7, 40418–40436. [CrossRef]

50. Gagnon, K.T.; Li, L.; Chu, Y.; Janowski, B.A.; Corey, D.R. RNAi factors are present and active in human cell nuclei. *Cell Rep.* 2014, 6, 211–221. [CrossRef]

51. Sharma, N.R.; Wang, X.; Majerciak, V.; Ajiro, M.; Kruhlak, M.; Meyers, C.; Zheng, Z.M. Cell Type- and Tissue Context-dependent Nuclear Distribution of Human Ago2. *J. Biol. Chem.* 2016, 291, 2302–2309. [CrossRef] [PubMed]

52. Kaelin, W.G., Jr. Common pitfalls in preclinical cancer target validation. *Nat. Rev. Cancer* 2017, 17, 425–440. [CrossRef] [PubMed]

53. Huang, H.T.; Seo, H.S.; Zhang, T.; Jiang, B.; Li, Q.; Buckley, D.L.; Nabet, B.; Roberts, J.M.; Paulk, J.; et al. MELK is not necessary for the proliferation of basal-like breast cancer cells. *Elife* 2017, 6, e26693. [CrossRef] [PubMed]

54. Lin, A.; Giuliano, C.J.; Sayles, N.M.; Sheltzer, J.M. CRISPR/Cas9 mutagenesis invalidates a putative cancer dependency targeted in on-going clinical trials. *Elife* 2017, 6, e24179. [CrossRef] [PubMed]

55. Giuliano, C.J.; Lin, A.; Smith, J.C.; Palladino, A.C.; Sheltzer, J.M. MELK expression correlates with tumor mitotic activity but is not required for cancer growth. *Elife* 2018, 7, e32838. [CrossRef] [PubMed]

56. Settleman, J.; Sawyers, C.L.; Hunter, T. Challenges in validating candidate therapeutic targets in cancer. *Elife* 2018, 7, e32402. [CrossRef]

57. Lu, H.; He, Y.; Lin, L.; Qi, Z.; Ma, L.; Li, L.; Su, Y. Long non-coding RNA MALAT1 modulates radiosensitivity of HR-HPV+ cervical cancer via sponging miR-145. *Tumour Biol.* 2016, 37, 1683–1691. [CrossRef]

58. Jin, C.; Yan, B.; Lu, Q.; Lin, Y.; Ma, L. The role of MALAT1/miR-1/slug axis on radioresistance in nasopharyngeal carcinoma. *Tumour Biol.* 2016, 4025–4033. [CrossRef]

59. Zhang, Y.; Chen, Z.; Li, M.J.; Guo, H.Y.; Jing, N.C. Long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 regulates the expression of Gli2 by miR-202 to strengthen gastric cancer progression. *Biomed. Pharmacother.* 2017, 85, 264–271. [CrossRef] [PubMed]

60. Li, Q.; Zhang, C.; Chen, R.; Xiong, H.; Qiu, F.; Liu, S.; Zhang, M.; Wang, F.; Wang, Y.; Zhou, X.; et al. Disrupting MALAT1/miR-200c sponge decreases invasion and migration in endometrioid endometrial carcinoma. *Cancer Lett.* 2016, 383, 28–40. [CrossRef]

61. Wang, S.H.; Zhang, W.J.; Wu, X.C.; Zhang, M.D.; Weng, M.Z.; Zhou, D.; Wang, J.D.; Quan, Z.W. Long non-coding RNA Malat1 promotes gallbladder cancer development by acting as a molecular sponge to regulate miR-206. *Oncotarget* 2016, 7, 37857–37867. [CrossRef] [PubMed]

62. Hou, Z.; Xu, X.; Zhou, L.; Fu, X.; Tao, S.; Zhou, J.; Tan, D.; Liu, S. The long non-coding RNA MALAT1 promotes the migration and invasion of hepatocellular carcinoma by sponging miR-204 and releasing SIRT1. *Tumour Biol.* 2017, 39, 1010428317718135. [CrossRef] [PubMed]

63. Laugesen, A.; Hojfeldt, J.W.; Helin, K. Role of the Polycomb Repressive Complex 2 (PRC2) in Transcriptional Regulation and Cancer. *Cold Spring Harb. Perspect. Med.* 2016, 6, a026575. [CrossRef] [PubMed]

64. Gupta, R.A.; Shah, N.; Wang, K.C.; Kim, J.; Horlings, H.M.; Wong, D.J.; Tsai, M.C.; Hung, T.; Argani, P.; Rinn, J.L.; et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature* 2010, 464, 1071–1076. [CrossRef] [PubMed]

65. Huang, K.B.; Zhang, S.P.; Zhu, Y.J.; Guo, C.H.; Yang, M.; Liu, J.; Xia, L.G.; Zhang, J.F. Hotair mediates tumorigenesis through recruiting EZH2 in colorectal cancer. *J. Cell. Biochem.* 2018. [CrossRef] [PubMed]

66. Battistelli, C.; Sabarese, G.; Santangelo, L.; Montaldo, C.; Gonzalez, F.J.; Tripodi, M.; Cicchini, C. The IncRNA HOTAIR transcription is controlled by HNF4alpha-induced chromatin topology modulation. *Cell Death Differ.* 2018. [CrossRef] [PubMed]

67. Chen, W.M.; Chen, W.D.; Jiang, X.M.; Jia, X.F.; Wang, H.M.; Zhang, Q.J.; Shu, Y.Q.; Zhao, H.B. HOX transcript antisense intergenic RNA represses E-cadherin expression by binding to EZH2 in gastric cancer. *World J. Gastroenterol.* 2017, 23, 6100–6110. [CrossRef] [PubMed]

68. Fan, Y.; Shen, B.; Tan, M.; Mu, X.; Qin, Y.; Zhang, F.; Liu, Y. TGF-beta-induced upregulation of malat1 promotes bladder cancer metastasis by associating with suz12. *Clin. Cancer Res.* 2014, 20, 1531–1541. [CrossRef]
69. Hirata, H.; Hinoda, Y.; Shahryari, V.; Deng, G.; Nakajima, K.; Tabatabai, Z.L.; Ishii, N.; Dahiya, R. Long Noncoding RNA MALAT1 Promotes Aggressive Renal Cell Carcinoma through Ezh2 and Interacts with miR-205. Cancer Res. 2015, 75, 1322–1331. [CrossRef]

70. Wang, D.; Ding, L.; Wang, L.; Zhao, Y.; Sun, Z.; Karnes, R.J.; Zhang, J.; Huang, H. LncRNA MALAT1 enhances oncogenic activities of EZH2 in castration-resistant prostate cancer. Oncotarget 2015, 6, 41045–41055. [CrossRef]

71. Qi, Y.; Ooi, H.S.; Wu, J.; Chen, J.; Zhang, X.; Tan, S.; Yu, Q.; Li, Y.Y.; Kang, Y.; Li, H.; et al. MALAT1 long ncRNA promotes gastric cancer metastasis by suppressing PCDH10. Oncotarget 2016, 7, 12693–12703. [CrossRef]

72. Kim, S.H.; Kim, S.H.; Yang, W.I.; Kim, S.J.; Yoon, S.O. Association of the long non-coding RNA MALAT1 with the polycomb repressive complex pathway in T and NK cell lymphoma. Oncotarget 2017, 8, 31305–31317. [CrossRef] [PubMed]

73. Wang, Y.; Xie, Y.; Li, L.; He, Y.; Zheng, D.; Yu, P.; Yu, L.; Tang, L.; Wang, Y.; Wang, Z. EZH2 RIP-seq Identifies Tissue-specific Long Non-coding RNAs. Curr. Gene Ther. 2018, 18, 275–285. [CrossRef] [PubMed]

74. Wang, X.; Goodrich, K.J.; Gooding, A.R.; Naeeem, H.; Archer, S.; Paucek, R.D.; Youmans, D.T.; Cech, T.R.; Davidovich, C. Targeting of Polycomb Repressive Complex 2 to RNA by Short Repeats of Consecutive Guanines. Mol. Cell 2017, 65, 1056–1067.e5. [CrossRef] [PubMed]

75. Davidovich, C.; Zheng, L.; Goodrich, K.J.; Cech, T.R. Promiscuous RNA binding by Polycomb repressive complex 2. Nat. Struct. Mol. Biol. 2020, 27, 1250–1257. [CrossRef] [PubMed]

76. Ji, Q.; Liu, X.; Fu, X.; Zhang, L.; Sui, H.; Zhou, L.; Sun, J.; Cai, J.; Qin, J.; Ren, J.; et al. Resveratrol inhibits invasion and metastasis of colorectal cancer cells via MALAT1 mediated Wnt/beta-catenin signal pathway. PLoS ONE 2013, 8, e78700. [CrossRef] [PubMed]

77. Ying, L.; Chen, Q.; Wang, Y.; Zhou, Z.; Huang, Y.; Qiu, F. Upregulated MALAT-1 contributes to bladder cancer cell migration by inducing epithelial-to-mesenchymal transition. Mol. Biosyst. 2012, 8, 2289–2294. [CrossRef] [PubMed]

78. Liang, J.; Liang, L.; Ouyang, K.; Li, Z.; Yi, X. MALAT1 induces tongue cancer cells’ EMT and inhibits apoptosis through Wnt/beta-catenin signaling pathway. J. Oral Pathol. Med. 2017, 46, 98–105. [CrossRef]

79. Malakar, P.; Shilo, A.; Mogilevsky, A.; Stein, I.; Pikarsky, E.; Nevo, Y.; Benyamini, H.; Elgavish, S.; Zong, X.; Prasanth, K.V.; et al. Long Noncoding RNA MALAT1 Promotes Hepatocellular Carcinoma Development by SRSF1 Upregulation and mTOR Activation. Cancer Res. 2017, 77, 1155–1167. [CrossRef] [PubMed]

80. Zhou, X.; Liu, S.; Cai, G.; Kong, L.; Zhang, T.; Ren, Y.; Wu, Y.; Mei, M.; Zhang, L.; Wang, X. Long Non Coding RNA MALAT1 Promotes Tumor Growth and Metastasis by inducing Epithelial-Mesenchymal Transition in Oral Squamous Cell Carcinoma. Sci. Rep. 2015, 5, 15972. [CrossRef]

81. Ji, D.G.; Guan, L.Y.; Luo, X.; Ma, F.; Yang, B.; Liu, H.Y. Inhibition of MALAT1 sensitizes liver cancer cells to 5-flurouracil by regulating apoptosis through IKKalpha/NF-kappaB pathway. Biochem. Biophys. Res. Commun. 2018, 501, 33–40. [CrossRef] [PubMed]

82. Jin, Y.; Feng, S.J.; Qiu, S.; Shao, N.; Zheng, J.H. LncRNA MALAT1 promotes proliferation and metastasis in epithelial ovarian cancer via the PI3K-AKT pathway. Eur. Rev. Med. Pharmacol. Sci. 2017, 21, 3176–3184. [PubMed]

83. Chen, Y.; Huang, W.; Sun, W.; Zheng, B.; Wang, C.; Luo, Z.; Wang, J.; Yan, W. LncRNA MALAT1 Promotes Cancer Metastasis in Osteosarcoma via Activation of the PI3K-Akt Signaling Pathway. Cell. Physiol. Biochem. 2018, 51, 1313–1326. [CrossRef] [PubMed]

84. Hu, L.; Wu, Y.; Tan, D.; Meng, H.; Wang, K.; Bai, Y.; Yang, K. Up-regulation of long noncoding RNA MALAT1 contributes to proliferation and metastasis in esophageal squamous cell carcinoma. J. Exp. Clin. Cancer Res. 2015, 34, 7. [CrossRef] [PubMed]