

Malat-1 may interact with several tumor suppressor and DNA repair genes and result in cancer

Divya Khatri and Kiran Kumar Battula*

Keshav Memorial Institute of Commerce and Sciences, Hyderabad – 500029

*Corresponding author

ABSTRACT

Malat-1 is a long non-coding RNA (lncRNA) over-expressed in several types of cancers. In a large number of studies, its interaction was shown with several micro-RNAs, the degradation of which results in the de-repression of the genes causing cancers. As lncRNAs are known to regulate gene expression by diverse mechanisms, here in the present study we addressed by *insilico* methods of whether Malat-1 lncRNA has any interaction to sponge away the mRNA of genes, whose repression may lead to cancers. Through these studies, we predicted that Malat-1 lncRNA could interact with the mRNA of several tumor suppressor genes and genes of DNA repair mechanisms. Further *in vitro/in vivo* studies can lead to a better understanding of these mechanisms and hence on therapeutic aspects.

Received: Dec 05, 2022 | **Accepted:** Jan 02, 2023 | **Published:** Jan 05, 2023

Keywords: Malat-1, lncRNA, cancer, tumor suppressor genes, DNA repair genes

Citation: Divya Khatri and Kiran Kumar Battula (2023) Malat-1 may interact with several tumor suppressor and DNA repair genes and result in cancer. KMICS Journal of Sciences 1(1): 1-9. DOI: <https://doi.org/10.62011/kmicsjs.2023.1.1.2>

Competing interests: The authors have declared that no competing interests exist.

Copyright: © 2023 Divya Khatri and Kiran Kumar Battula. This is an open-access article. The use, distribution, and reproduction of this article in any medium is unrestricted, provided the original author and source are cited.

INTRODUCTION

LncRNA, are long non-coding RNAs, of about 200 nucleotides or more in length and some times they may be as long as 100kb^{1,2}. Like protein-coding genes, they are transcribed by DNA Polymerase II, and most of them are capped, spliced, and polyadenylated³⁻⁷. Though generally they are non-coding RNA, some of them have coding potential and code for small functional peptides⁸⁻¹⁰. LncRNAs account for more than 16000 genes in mammalian genome, and their major role has been ascribed to regulate gene expression¹¹⁻¹⁵. They employ diverse methods to regulate gene regulation. They may bind to miRNA, mRNA, and even transcription factors and chromatin remodeling proteins to regulate gene expression¹⁶⁻²¹.

Metastasis-associated lung adenocarcinoma transcript (MALAT)-1 is one of the first cancer-associated lncRNAs to be identified²². It was found to be overexpressed in various types of cancers like nonsmall cell lung cancer (NSCLC), hepatocellular carcinoma, cervical cancer, osteosarcoma, glioblastoma, colorectal cancer, and other cancers²³⁻²⁹. Malat1 is known to be involved in the modulation of several molecular signaling pathways such as MAPK/ERK, PI3K/AKT, WNT/ β -catenin, and NF- κ B³⁰⁻³⁴. Therefore malat-1 may have a wide spectrum of interactions. In fact, several studies have shown that Malat-1 interacts with different miRNA, all of which represses the genes causing cancers³⁵.

While malat-1 and miRNA interactions are well known, the direct interaction of Malat-1 with mRNA in the context of cancers is not adequately addressed. Therefore in the present study, through bioinformatics tools, we assessed whether malat-1 has any direct interaction with the mRNA of any of the ‘tumor suppressor genes’, and further with the mRNA of any of the ‘DNA repair genes’ both the types being known to be reduced in cancers.

MATERIALS AND METHODS

I. Data mining:

Step1: Tumor suppressor genes and genes for DNA repair mechanisms were obtained from the ‘Gene’ database of the NCBI website (<https://www.ncbi.nlm.nih.gov>) by providing the respective search words.

Step2: Ensembl IDs for the above genes were obtained from the ‘Ensembl’ website (<https://www.ensembl.org>) by providing the gene symbols obtained from NCBI. Ensembl ID for ‘Malat-1’ lncRNA was also obtained in a similar way.

II. Assessment of Interaction of lncRNA with mRNA of the target genes

“LncRRISearch”, available at ‘<http://rtools.cbrc.jp/LncRRISearch>’ was used to predict the interaction of lncRNA sequence with the mRNA of a target gene upon provision of their ensembl IDs at respective search bars. The tool also provides the length of interaction between the two.

RESULTS

Identification and Shortlisting of ‘Tumor Suppressor Genes’ and genes responsible for ‘DNA repair mechanisms’.

Through the search results from the ‘Gene’ and ‘Pubmed’ databases of NCBI, we have shortlisted 130 genes for the category of tumor suppressor genes and 411 genes for the category of DNA repair genes.

Assessment of interaction of Malat-1 with the above genes

Fifty-five out of 130 tumor suppressor genes (TSGs), and 194/411 DNA repair genes (DRGs) were predicted to interact with the malat 1 gene. Twenty-eight of the DNA repair genes, which were predicted to interact with malat-1, were also found in the list of tumor suppressor genes. Therefore three groups of genes were made which are (i) unique TSGs, (ii) unique DRGs, and (iii) genes common for TSGs & DRGs. Based on the predictions of length of Interaction, the genes were arbitrarily grouped as high (50 bp and above), moderate (18bp-49bp) and low (<18bp) interacting. Among the unique TSGs, 4 genes were predicted as highly interacting, 22 were predicted as moderately interacting and one gene as low interacting. Among the unique DRGs, 40 were predicted as highly interacting, 121 were predicted as moderately interacting, and 5 as low interacting. Among the common genes for TSG and DRG, 7 were predicted as highly interacting, and 21 were predicted as moderately interacting (Table 1).

Table 1: Interaction of Malat-1 with Tumor suppressor genes and DNA repair genes

Unique Tumor suppressor genes (TSGs)	
High interaction	ZFHX3, EI24, KMT2D, XIRP1
Moderate Interaction	CYLD,ERBB4,TBX3,TIMP3,TRIB2,POU2F3,SORBS3,ZAP70,PTGS2,RPS6KA6,CHD4,CTNNA3,SMARCB1,DNMT3B,NF1,CDKN1B,CSRNP1,CLDN2,ZFP36,DIDO1,RET,TNFRSF10B
Low Interaction	ID1
Unique DNA repair genes (DRGs)	
High Interaction	HIC1,NONO,SOX4,DTNA,PRRX1,CDK9,CD4,PIK3R2,POGZ,ATXN3,SMAD2,HNRNPA1,TRIP12,RFC2,HDAC10,XIST,CDK12,MYB,RUNX1,ARRB1,CUX1,LMNA,NCOR2,ASCC1,HUWE1,IRS1,EWSR1,PHF2,POLR2A,ERG,POLK,RUVBL2,KAT5,RPS6KA3,SETD2,UBR5,SQSTM1,XRCC1,CHD2,MAPK3
Moderate Interaction	CEP164,ERCC6,FGF2,KIF16B,BCR,DROSHA,EP300,TRRAP,MAPK8,ATM,FTO,IGF1R,PML,TBX20,TREX1,ARID1B,GEMIN4,KMT2C,VDR,DDR1,DDX3X,E2F1,FUS,NIPBL,WT1,ARID1A,MACROD2,POLE,MTUS1,TDP1,XRCC3,PGK1,SPARC,SPTAN1,TET2,ARID2,RAD50,CDK4,DUOX2,NKX2-1,RAD51,RAG2,SRSF2,BBC3,CLU,CREBBP,EYA1,MRE11A,POLG,SRC,TK2,AKT3,GSK3B,MACF1,RAD54L,SERPINE1,ARL11,DEK,ERCC1,ESR1,MSMT1R,NR1H3,RELA,SLX4,SMCHD1,TRAF3,BCL2,CCND1,CREB1,TP63,UBA1,ABL1,ACLY,FOS,KRAS,MCM3AP,NPM1,SREBF1,VAV2,BUB1B,EYA2,FANCD2,REV3L,RORC,SOX2,ATXN7,CLIP1,EIF4G1,SMC1A,TERT,HNRNPC,POLL,ATRX,CDK6,CEBPA,ENG,GAPDH,NCOA3,PAK4,VEGFA,ATF3,ING1,APPL2,KIF1A,MGMT,RAD51C,ATR,PIM1,CDK5RAP2,CHRNA4,MAPK1,MPLKIP,SNCA,DICER1,ROCK1,SUZ12,PDS5B,CSNK2A1,GFI1,FANCA,UBC
Low Interaction	POLN,SMO,SYNE2,UBE2B,HTT
Genes common for TSGs & DRGs group	
High interaction	DNMT3A,SIRT1,AR,EGR1,DOT1L,SP1,YY1

Moderate Interaction	SMAD3,PTCH1,STAT3,CDKN1A,CDKN2A,CHEK2,MBD1,SMAD4,KDM5B,EYA4,PTEN,BRAF,TGFB1,FBXW7,TP73,MYC,MTHFR,TP53,PBRM1,HNRNPA2B1,DNMT1
Low Interaction	-

DISCUSSION & CONCLUSION

It has been well established that tumor suppressor genes and several of the DNA repair genes are downregulated in cancer conditions (Tables 2, 3). For several of these genes, the mechanisms causing their downregulation, and further the pathways affected are also known. However, as new markers are discovered, they lead to a better understanding on the previous mechanisms. Malat-1 being a relatively new marker needs an exploration of its interaction with all the known genes, whose repression may lead to cancer. While *invivo* and *invitro* studies have led to understanding of its interaction with several genes, they are limited to a specific genome variant and a specific prevailing environment. The present bioinformatic analysis attempts to predict Malat-1 interaction with its target genes without such biases. The present work enlists a large number of genes of TSGs, and DRGs groups, which are likely to interact with Malt-1. Validation of these interactions through *invitro* studies may lead to discovery of new markers and hence novel therapeutic targets.

Table 2: Tumor Suppressor Genes reported as downregulated in various cancers

Gene	Cancer type	Reference
ZFHX3	prostate cancer	PMID: 34953044
KMT2D	lung tumorigenesis	PMID: 32243837
CLDN2	cancer, primary tumor cells	PMID: 31726679;PMID: 30349422
EI24	Esophageal squamous cell carcinoma, epithelial tumor cells	PMID: 32974192;PMID: 24280371
POU2F3	Small cell lung cancer	PMID: 35760287
RPS6KA6	endometrial cancer	PMID: 21372219
AR	breast cancer	PMID: 29912871
CDKN1A	breast cancer	PMID: 31169265
CDKN2A	colon cancer	PMID: 25879218
CHEK2	breast and other cancers	PMID: 34903604
DNMT1	esophageal cancer	PMID: 30735457
DOT1L	ovarian cancer	PMID: 30899413
EGR1	breast cancer	PMID: 34488929

CYLD	melanoma	PMID: 34497368
CDKN1B	colorectal cancer	PMID: 26114183
HNRNPA2B1	colorectal cancer	PMID: 32698890
ID1	adenocarcinoma gastric cell line	PMID: 23900621
KDM5B	breast cancer, acute myeloid leukemia(AML)	PMID: 32003509;PMID: 35217626
PBRM1	cancers	PMID: 33888468
PTEN	head and neck cancers	PMID: 26916897
TIMP3	gastric cancer	PMID: 27314831
TP53	cancers	PMID: 27280975

Table 3: DNA Repair Genes reported as downregulated in cancers

Genes	cancer type	Reference
AKT3	Ovarian cancer	PMID: 31703725
AR	Breast cancer	PMID: 29912871
ARID1A	Several cancers	PMID: 26384299
ATM	Colon cancer	PMID: 34369561
BBC3	Head and Neck cancer	PMID: 23220852
BCL2	Breast cancer cells	PMID: 8174112
CDKN1A	Breast cancer	PMID: 31169265
CDKN2A	Colon cancer	PMID: 25879218
CHEK2	Breast and Other cancers	PMID: 34903604
DNMT1	Esophageal cancer	PMID: 30735457
DOT1L	Ovarian cancer	PMID: 30899413
EGR1	Breast cancer	PMID: 34488929
HNRNPA2B1	Colorectal cancer	PMID: 32698890
KDM5B	Breast cancer, Acute myeloid leukemia(AML)	PMID: 32003509;PMID: 35217626
PBRM1	Cancers	PMID: 33888468
PTEN	Head and Neck cancers	PMID: 26916897
TP53	Cancers	PMID: 27280975

REFERENCES

1. Gutschner T, Hammerle M, Diederichs S. MALAT1 – a paradigm for long noncoding RNA function in cancer. *J Mol Med (Berl)*. 2013;91(7):791–801.
2. Qiu MT, Hu JW, Yin R, Xu L. Long noncoding RNA: an emerging paradigm of cancer research. *Tumour Biol*. 2013;34 (2):613–620.
3. Derrien T, Johnson R, Bussotti G, et al. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. *Genome Res*. 2012;22(9):1775-1789. [PMCID: PMC3431493] [PubMed: 22955988]
4. Novikova IV, Hennelly SP, Sanbonmatsu KY. Sizing up long non-coding RNAs: Do lncRNAs have secondary and tertiary structure? *Bioarchitecture*. 2012;2[6]:189-199. [PMCID: PMC3527312] [PubMed: 23267412]
5. Guttman M, Amit I, Garber M, et al. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. *Nature*. 2009;458[7235]:223-227. [PMCID: PMC2754849] [PubMed: 19182780]
6. Gibb EA, Brown CJ, Lam WL. The functional role of long non-coding RNA in human carcinomas. *Mol Cancer*. 2011;10:38. [PMCID: PMC3098824] [PubMed: 21489289]
7. Sigova AA, Mullen AC, Molinie B, et al. Divergent transcription of long noncoding RNA/mRNA gene pairs in embryonic stem cells. *Proc Natl Acad Sci USA*. 2013;110[8]:2876-2881. [PMCID: PMC3581948] [PubMed: 23382218]
8. Slavoff, S.A.; Mitchell, A.J.; Schwaid, A.G.; Cabili, M.N.; Ma, J.; Levin, J.Z.; Karger, A.D.; Budnik, B.A.; Rinn, J.L.; Saghatelian, A. Peptidomic Discovery of Short Open Reading Frame-Encoded Peptides in Human Cells. *Nat. Chem. Biol*. 2013, 9, 59–64.
9. Anderson, D.M.; Anderson, K.M.; Chang, C.L.; Makarewich, C.A.; Nelson, B.R.; McAnally, J.R.; Kasaragod, P.; Shelton, J.M.; Liou, J.; Bassel-Duby, R.; et al. A Micropeptide Encoded by a Putative Long Noncoding RNA Regulates Muscle Performance. *Cell* **2015**, 160, 595–606.
10. Wang, L.; Fan, J.; Han, L.; Qi, H.; Wang, Y.; Wang, H.; Chen, S.; Du, L.; Li, S.; Zhang, Y.; et al. The Micropeptide LEMP Plays an Evolutionarily Conserved Role in Myogenesis. *Cell Death Dis*. **2020**, 11.
11. Howe, K.L.; Achuthan, P.; Allen, J.; Allen, J.; Alvarez-Jarreta, J.; Amode, M.R.; Armean, I.M.; Azov, A.G.; Bennett, R.; Bhai, J.; et al. Ensembl 2021. *Nucleic Acids Res*. **2021**, 49.
12. Dinger, M.E.; Amaral, P.P.; Mercer, T.R.; Pang, K.C.; Bruce, S.J.; Gardiner, B.B.; Askarian-Amiri, M.E.; Ru, K.; Solda, G.; Simons, C.; et al. Long Noncoding RNAs in Mouse Embryonic Stem Cell Pluripotency and Differentiation. *Genome Res*. **2008**, 18, 1433–1445.
13. Sun, M.; Kraus, W.L. From Discovery to Function: The Expanding Roles of Long NonCoding RNAs in Physiology and Disease. *Endocr. Rev*. **2015**, 36, 25–64.

14. Peschansky, V.J.; Wahlestedt, C. Non-Coding RNAs as Direct and Indirect Modulators of Epigenetic Regulation. *Epigenetics* **2014**, *3*, 3–12.
15. Zhang, P.; Wu, W.; Chen, Q.; Chen, M. Non-Coding RNAs and Their Integrated Networks. *J. Integr. Bioinform.* **2019**, *16*, 1–12.
16. Sun, M.; Kraus, W.L. From Discovery to Function: The Expanding Roles of Long NonCoding RNAs in Physiology and Disease. *Endocr. Rev.* **2015**, *36*, 25–64.
17. Chaumeil, J.; Le Baccon, P.; Wutz, A.; Heard, E. A Novel Role for Xist RNA in the Formation of a Repressive Nuclear Compartment into Which Genes Are Recruited When Silenced. *Genes Dev.* **2006**, *20*, 2223–2237.
18. 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.
19. Kazimierczyk, M.; Kasproicz, M.K.; Kasprzyk, M.E.; Wrzesinski, J. Human Long Noncoding RNA Interactome: Detection, Characterization and Function. *Int. J. Mol. Sci.* **2020**, *21*, 1027.
20. Moore, I.V.; Joseph, B.; Uchida, S. Functional Characterization of Long Non-Coding RNAs. *Joseph. Curr. Opin. Cardiol.* **2020**, *35*, 199–206.
21. Panni, S.; Lovering, R.C.; Porras, P.; Orchard, S. Non-Coding RNA Regulatory Networks. *Biochim. Biophys. Acta Gene Regul. Mech.* **2020**, *1863*, 194417.
22. Ji P, Diederichs S, Wang W, 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(39):8031-8041. [PubMed: 12970751]
23. Ji P, Diederichs S, Wang W, 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(39):8031–8041.
24. Guerrieri F. Long non-coding RNAs era in liver cancer. *World J Hepatol.* 2015;7(16):1971–1973.
25. Xu Y, Zhang Q, Lin F, et al. Casiopeina IIgly acts on lncRNA MALAT1 by miR175p to inhibit FZD2 expression via the Wnt signaling pathway during the treatment of cervical carcinoma. *Oncol Rep.* 2019;1.
26. Fang D, Yang H, Lin J, et al. 17beta-estradiol regulates cell proliferation, colony formation, migration, invasion and promotes apoptosis by upregulating miR-9 and thus degrades MALAT-1

in osteosarcoma cell MG-63 in an estrogen receptor-independent manner. *Biochem Biophys Res Commun.* 2015;457(4):500–506.

27. Li H, Yuan X, Yan D, et al. Long Non-Coding RNA MALAT1 Decreases the Sensitivity of Resistant Glioblastoma Cell Lines to Temozolomide. *Cell Physiol Biochem.* 2017;42(3):1192–1201.

28. Wu S, Sun H, Wang Y, et al. MALAT1 rs664589 Polymorphism Inhibits Binding to miR-194-5p, Contributing to Colorectal Cancer Risk, Growth, and Metastasis. *Cancer Res.* 2019;79(20):5432–5441.

29. Gao D, Lv AE, Li HP, Han DH, Zhang YP. LncRNA MALAT-1 Elevates HMGB1 to Promote Autophagy Resulting in Inhibition of Tumor Cell Apoptosis in Multiple Myeloma. *J Cell Biochem.* 2017;118(10):3341–3348

30. Liu S, Yan G, Zhang J, Yu L. Knockdown of Long Noncoding RNA (lncRNA) Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) Inhibits Proliferation, Migration, and Invasion and Promoted Apoptosis By Targeting miR-124 in Retinoblastoma. *Oncol Res.* Epub 21 May 2017.

31. Chen L, Feng P, Zhu X, et al. Long non-coding RNA Malat1 promotes neurite outgrowth through activation of ERK/MAPK signalling pathway in N2a cells. *J Cell Mol Med.* 2016;20(11):2102–2110.

32. Dong Y, Liang G, Yuan B, et al. MALAT1 promotes the proliferation and metastasis of osteosarcoma cells by activating the PI3K/Akt pathway. *Tumor Biology.* 2015;36(3):1477–1486.

33. Liang J, Liang L, Ouyang K, Li Z, Yi X. MALAT1 induces tongue cancer cells' EMT and inhibits apoptosis through Wnt/ β -catenin signaling pathway. *J Oral Pathol Med.* 2017;46(2):98–105.

34. Zhao G, Su Z, Song D, Mao Y, Mao X. The long noncoding RNA MALAT1 regulates the lipopolysaccharide-induced inflammatory response through its interaction with NF- κ B. *FEBS Lett.* 2016;590(17):2884–2895.

35. Fu S, Wang Y, Li H, Chen L, Liu Q. Regulatory Networks of LncRNA MALAT-1 in Cancer. *Cancer Manag Res.* 2020 Oct 15;12:10181-10198. doi: 10.2147/CMAR.S276022. PMID: 33116873; PMCID: PMC7575067.