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MiR-4492, a New Potential MicroRNA for Cancer Diagnosis and Treatment: A Mini Review

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There is no doubt that the incidence of cancer sufferers is rising in the world, and it is estimated that in the next several decades, the number of people suffering from malignancies or the cancer rate will double. Diagnostic and therapeutic targeting of noncoding RNAs (ncRNAs), especially microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), represent an excellent approach for cancer diagnosis and treatment, as well as many other diseases. One of the latest miRNAs is miR-4492, upregulating some genes in tumor tissues including ROMO1, HLA-G, NKIRAS2, FOXK1, and UBE2C. It represents an attractant example of a miRNA acting at multiple levels to affect the same malignancy hallmark. Based on the studies, miR-4492 plays a key role in several cancers such as, breast cancer, bladder cancer, osteosarcoma, glioblastoma multiforme, hepatocellular carcinoma, colorectal cancer, and ovarian cancer. Putting it all together, identifying the precise mechanisms of miR-4492 in the pathogenesis of cancer, could pave the way to find better diagnostic and therapeutic strategies for cancer sufferers. For this reason, it might be a novel potential diagnostic biomarker and therapeutic target for neoplasms.

Key Words: *MicroRNAs; Long Noncoding RNA; Neoplasms; miR-4492*

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INTRODUCTION

One of the most important responsible for the majority of global deaths is non-communicable diseases,[1] and cancer is estimated become as the major death cause and the most critical obstacle to enhancing life span all over the world in the 21st century. Neoplasms include several diseases in which the major factor is the uncontrolled cell proliferation, invasion, and diffusion of cancerous cells from primary spot to the other organs.[2] In a malignant tumor, cells are immensely dissimilar to typical cells, both physiologically and morphologically.[2] It is proven that cancers are the second major cause of mortality in developing nations and, also are the major death cause in industrialized nations.[2] The essential genes that participate in neoplasms are generally categorized into five major groups: 1) proto-carcinogens (proto-oncogenes), 2) DNA repairing genes, 3) tumor suppressor genes, 4) genes associated with apoptosis, and 5) genes associated with telomere homeostasis.[2] Furthermore, the other crucial factor that scientists consider as a critical part of beginning and deteriorating numerous diseases, especially neoplasms is increasing oxidative stress.[2-4] Scientists and clinical practitioners have applied numerous biomarkers for therapeutic, diagnostic, and prognostic assessment of neoplasms. Due to heterogeneity in the precise molecular and cellular mechanisms in cancerous cells, novel biomarkers are always required.

Noncoding RNAs (ncRNAs) are originated from the greater constituent of the genome that do not encode any amino acid sequence though create noncoding transcripts that adjust the function and expression of genes and proteins. MicroRNAs (miRNAs) and long ncRNAs (lncRNAs) are the two important types of ncRNAs the well-studied and the more lately verified. Deregulation of miRNAs and lncRNAs has been associated to neoplasm scrutinize to date and influences all critical neoplasm aspects.[5-7] As mention before, miRNAs are a great and critical class of small noncoding RNAs found in various organisms including plants, animals, and also in some viruses, which in-

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versely regulate expression of coding genes at the mRNA level.[8] Let-7 was the first human miRNA and it was introduced in 2000,[8,9] and for the present approximately more than 1,900 human mature miRNAs have been identified and illustrated in the miRBase miRNA online database.[10] Most of mature miRNA sequences are positioned in exons or introns of ncRNAs along with introns of pre-mRNA.[11] RNA polymerase II (Pol II) is responsible for transcription of many miRNAs genes as long primary miRNAs (pri-miRNAs), the sequence that contains a small number of stem-loop structure made of about 70 nucleotides individually. Mature miRNAs are orientated to the 3' end of their target mRNA via base pairing, subsequently result in the destabilization and translational suppression of mRNA. It has been assessed that miRNAs modulate the expression of already one-third of the genes coding peptides and proteins.[10]

Two important roles are identified for miRNAs are regulation of the epigenetics modifiers, including DNA methyltransferases and targeting of epigenetic modifications (i.e., DNA methylation).[10] In addition, miRNA biological functions have been comprehensively investigated by the studies about transgenic up-regulation experiments and miRNA-knockout models.[12] Functional studies have shown the crucial function of miRNAs in several biological actions as metabolism, embryogenesis, developmental timings, apoptosis, cell differentiation, and organogenesis.[13] It has been recently recommended that miRNAs present in the circulation could possibly participate in inter- and intra-cellular communication.[14] MiRNAs have been suggested as diagnostic and therapeutic targets of numerous diseases.[10,15] Many research works have proved the major function of miRNAs in several cancer-associated mechanisms and pathways, like apoptosis, metabolism, proliferation, invasion, drug resistance, metastasis, and differentiation. The pathological route of malignancy has also been confirmed to be directly linked to the miRNAs dysregulation.[16] Furthermore, miRNAs could be specific to one or a few tissues. Moreover, many studies have shown that various neoplasms have distinguishing profiles regarding miRNA expression. Until now, the fundamental biogenesis and interactions of the intracellular miRNAs were examined in numerous subjects.[16] Alternatively, the presense of extracellular RNAs in circulation was introduced first by Bartel and several miRNAs are confirmed to be found in a stable cell-free condition in biofluids and other extracellular milieu, including plasma, seminal serum, ascites, saliva, urine, cerebrospinal fluid, and amniotic pleural effusions.[16-18]

The usage of miRNA-based diagnostics and therapeutics have advantages. MiRNAs play through targeting various genes within pathways, thus provoking a wider yet specific response. For example, one of the latest miRNAs introduced as miR-4492, upregulating several genes such as ROMO1, HLA-G, NKIRAS2, FOXK1, and UBE2C, constitutes a great example of a miRNA functioning at many levels to influence the same neoplasm hallmark.[7,19,20] For instance, miR-4492 upregulation as a ncRNA targeting HLA-G in trophoblasts is associated the secretion of extracellular vesicle secretion.[21] LncRNA FTX and UBE2C, upregulated in renal cell carcinoma (RCC) are crucial factors promoting proliferation, migration and invasion capacities in this neoplasms. The link between these two genes is miR-4429 which could block UBE2C and also be targeted by lncRNA TFX, providing an opportunity to develop a biomarker in RCC.[22] Additionally, miR-4492 sponged by hsa_circ_0000043 along with expression of BDNF and STAT3 are associated with 16HBE-T cell migrating, invading, and proliferating.[23] The usage and targeting of occurring miRNAs can be another bright approach to existing RNA-based therapies and diagnosis, and also might potentially promote diagnostic and therapeutic effects.[7]

As it is established, not all but only a portion of RNA pool is translated to proteins. This phenomenon brings the chance for some RNA interactions of same or different types, leading to more roles for RNA pool in cellular function. Luciferase reporter assay, as a functional test, is applied to measure assess intermolecular interactions. Recently, luciferase reporter assay has been adapted to evaluate the posttranscriptional regulation through miRNA–mRNA interactions.[24] Several works have used the 3'UTR of target genes downstream to the luciferase coding sequence and overexpressed the regulator miRNAs to analyze the effect of miRNA interaction on luciferase expression.[24,25] Using similar principle, protocols for dual-fluorescence assay have been established with constructs expressing mCherry with the miRNA target sequence to validate the effect of miRNA on target gene expression. This evaluation provides numerous advantages, including use of a larger sample size, promoting in time-course studies, and even being applied for high throughput techniques, thus making it a proper choice for understanding RNA–RNA interactions.[26] To start detecting the interaction between RNA and protein of target, cells expressing the protein are lysed. For RNA-dependent pull-down, the prepared lysate is incubated with streptavidin-based beads which are coated with a biotinylated lncRNA (lncRNA is synthesized and conjugated before). For RNA immunoprecipitation (RIP), lncRNA is co-precipitated with the protein of target from the lysate. In order to pull down lncRNAs in vitro, the immunopurified and immobilized protein is incubated with radiolabeled transcripts. Both RNA pull-down and RIP are of prevalently utilized since they are considered as simple, convenient, and low-cost techniques. However, contrary to immunoprecipitation methods, pull-down techniques are mostly beneficial in in vitro settings.[27,28]

In this mini review, we focus on the biological functions of miR-4492, interacting with lncRNAs, and also the role of this miRNA in neoplasms. In the following, association of miR-4492 with several neoplasms and its diagnostic and therapeutic potential will be discussed.

THE ROLE OF MIR-4492 IN NEOPLASMS

A new role named competing endogenous RNA (ceRNA) has been reported. This important phenomenon in post-transcriptional regulation of many kinds of RNAs (coding and noncoding) competing for the same pool of miRNA to regulate each other, therefore, it sounds significantly important in neoplasms. Generally lncRNAs are introduced as a sponge to miRNAs in order to limit their accessibility and consequently, control the expression of their target mRNAs.[29,30] The ongoing research to offer novel insight into the roles and interaciotns of ncRNAs in cancer is promising. The investigation of miR-4492 in cancer literature generally is mainly ill investigated. However, it is noteworthy to mention that some lncRNAs have also been evaluated along with miR-4492 to find their possible interactions. Here we mention a few examples of lncRNAs studied in various cancers and their relations with miR-4492 are assayed (Fig. 1).

Forkhead Box D2 adjacent opposite strand RNA 1 (FOXD2-AS1) is an lncRNA showing an overexpression in ovarian cancer, both in human cancer tissues and cancer cell lines.[31] FOXD2-AS1 is generally known as a tumor promoter/accelerator and predicts poor prognosis in some cancers.[32-36] This oncogene targets miR-4492 directly as a sponge via a mutual binding site (validated by lucifarese-based assay), hence they are negatively correlated. By a clinical approach, it is possible that FOXD2-AS1 could promote the cancer cells by reducing miR-4492 expression, the phenomenon which might be informative both in diagnosis and targeting of ovarian cancer.[31] Further analyses are needed to confirm this interaction since FOXD2-AS1 shows correlation with more ncRNAs, including miR-143,[33] miR-485-5p,[36] and miR-7-5p.[37] Additionally the sponge action of FOXD2-AS1 has been reported for other miRNAs (including miR-182-5p and miR-375) as well.[38,39] These phenomena add to the complexity of the action of these ncRNAs.

Long intergenic noncoding RNA 319 (LINC00319) is another noticed lncRNA, presenting a role in cancer cell progression, proliferation, metastasis, poor prognosis and metastasis.[40-43] It is also upregulated in bladder cancer tissue as well as bladder cancer cell lines and provokes cancer progression. The upregulated expression of this lncRNA is positively correlated to the stage of the cancer, and negatively correlated to the recurrence-free survival of the patients and the expression of miR-4492. Studies also has shown that the latter leads to the overexpression of reactive oxygen species modulator 1 (ROMO1).[44] Similar to FOXD2-AS1, LINC00319 has a targeting role for miR-4492 (confirmed by lucifarese-based assay, RNA pull down and immunoprecipitation) hence these ncRNAs show a direct correlation. MiR-4492 acts as a tumor suppressor gene in ovarian and bladder cancers. Accordingly, ROMO-1 is generally known as a possible target of this microRNA, a protein which acts as a progression accelerator in cancer.[45-47] It is reasonable to accept LINC00319/miR44-92 as a signaling axis that controls the expression of ROMO1.[44] It is noteworthy that inhibition of miR-4492 inverted the LINC00319 and FOXD2-AS1 suppression effects.[31,44]

Small nucleolar RNA host gene 22 (SNHG22) is another example of lncRNA showing connections with miR-4492 in cancer. The main role of SNHG22 in many neoplasms is ill investigated. Similar to the previously described lncRNAs, SNHG22 acts as a sponge for many miRNAs (including miR-2467,[48] miR-200c-3p,[49] and miR-4492,[50] the latter confirmed by RNA pull-down and RNA immunoprecipitation measures) in the cytoplasm. The expression of this lncRNA is downregulated in osteosarcoma, a phenomenon which is in accordance with activation of migration, proliferation,

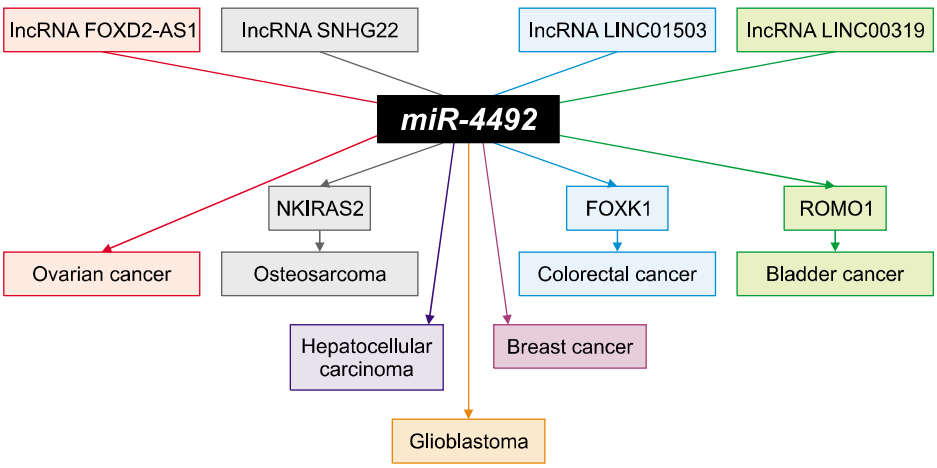

FIG. 1. The association of miR-4492 with several neoplasms. MiR-4492 acts a crucial role in several cancers such as breast cancer, bladder cancer, osteosarcoma, glioblastoma, hepatocellular carcinoma, colorectal cancer, and ovarian cancer, through various up-stream lncRNAs and down-stream protein genes. FOXD2-AS1: Forkhead Box D2 adjacent opposite strand RNA 1, SNHG22: small nucleolar RNA host gene 22, LINC01503: long intergenic non-protein coding RNA 1503, LINC00319: long intergenic noncoding RNA 319, NKIRAS2: NK-κB inhibitor-interacting Ras-like 2, FOXK1: Forkhead Box K1, ROMO1: reactive oxygen species modulator 1.

and invasion of osteosarcoma cells. Also the overexpression of SNHG22 inhibits crucial mechanisms in cancer, like epithelial-to-mesenchymal transition and angiogenesis.[50] It is also reported that miR-4492 regulates NK-κB inhibitor-interacting Ras-like 2 (NKIRAS2), a protein that regulates the activation of NF-kappa B by NK-kappa B inhibition.[51] The expression of NKIRAS2 is downregulated in osteosarcoma. These findings offers that this protein could be a direct target of miR-4492 and makes SNHG22 a proper target for the management of osteosarcoma. The downregulation effects of miR-4492 on NKIRAS2 mainly effects the protein level, indicating the effect of miR as a ceRNA in SNHG22-miR-4492- NKIRAS2 axis.[50]

The function of long intergenic non-protein coding RNA 1503 (LINC01503) in cancer together with miR-4492 has also been reported. The expression of this lncRNA is upregulated in many cancers including colorectal,[52] gastric cardia adenocarcinoma,[53] and glioma.[54] The oncogenic role of LINC01503 is tightly in relation with overexpression of a well-known oncogene, Forkhead Box K1 (FOXK1), a phenomenon that happens by LINC01503 sponging miR-4492. On this basis, miR-4492 is known as another direct target LINC01503 in neoplasms since it targets FOXK1 directly (validated by lucifarese-based assay).[52]

The benefits of miR-4492 assay is not limited to its expression in tumor tissues but it is useful to be assessed in plasma as a circulating RNA, providing a possibility to predict the therapy response in neoplasms. MiR-4492 is reported to be significantly associated with complete response (elevated in comparison to partial response) to transarterial chemoembolization in patients suffering hepatocellular carcinoma. Together with a combined assessment of specificity and sensitivity through a ROC curve, miR-4492 is offered as a promising biomarker, surpassing alpha-fetoprotein to predict response to transarterial chemoembolization.[55]

While most of the available data about miR-4492 supports the tumor suppressor role for this ncRNA, some evidence approve the contrary. All the findings on the tumor tissues are supported by cell culture evaluations, indicating that miR-4492 expression opposes tumor progression,[31,44,50,52] however, there are certain publications that offer an oncogenic role for this ncRNA. For instance, spheroid-enriched MCF-7 breast cells have shown some of the characteristics of cancer stem cells (i.e., cancer stem cell markers). These cells present the overexpression of mir-4492 (23 fold-change) simultaneously with chemoresistance, self-renewability, and metastasis.[56] These finding would attract more attention to miR-4492 since the expression of this miRNA has never been reported in breast cancer before, and unlike in cancers of ovary, bladder, colorectal, and osteosarcoma, miR-4492 might support oncogenesis in breast cancer. The elevated miR-4492 expression is reported in spheroid-enriched cells, which represent cancer stem cells (CSCs). It is noteworthy that CSCs are associated with the relapses of neoplasms (including self-renewal and chemoresistance capabilities) and eventually, metastasis. In other words, elevated expression on miR-4492 is reported in a specific model, which does not happen in every breast cancer case. In addition, clinical evidence are needed to further evaluate these in vitro (spheroid culture) findings. Such phenomenon is reported regarding glioblastoma. It is proposed that miR-4492 could be a new prognostic biomarker of brain cancer, especially glioblastoma, which is activated in necrosis.[57] Further, the elevated expression of this ncRNA is reversely correlated with the expression of genes acting as focal adhesion.

FUTURE DIRECTION AND CHALLENGES

More effective integration of data-driven and expert-driven strategies for biomarker discovery and identification is seen as key to improved success. Despite the various studies have been carried out on mir-4492, it must go through different steps to reach a clinical biomarker. First, its relationship with other lncRNAs and proteins that play a pivotal role in inhibiting or launching neoplasms should be investigated using more and stronger bioinformatics software. Secondly, these relationships should be proven by in vitro and in vivo studies. Then, it should be measured in various populations with different age groups on several diseases, both in tissue and plasma, and eventually a cutoff would be determined. After going through these steps, mir-4492 might be used as a clinical biomarker for diagnosis and treatment of neoplasms.

CONCLUSION AND PERSPECTIVES

Since the first ncRNAs uncovering, especially miRNAs, there has been a noticeable count of research evaluated their biological roles and the potential of biomarkers for cancer diagnosis and treatment. As we described here, miR-4492 has been proven to contribute in several malignancies opposing the tumorigenesis and development of cancerous cells. However, it is mandatory to examine this ncRNA in different stages of neoplasms and various specimens (i.e., plasma and urine) to reach a better insight on its value. For this reason, identifying the exact mechanisms of miR-4492 in the pathogenesis of cancer, might pave the way to find better diagnostic and therapeutic strategies for cancer. Further, miRNA-4492 could be a novel potential diagnostic biomarker and therapeutic target for malignancy. Moreover, the prosperous utilization of RNA-based diagnostics and therapeutics demands an extraordinary multidisciplinary manner, including methodological promotion in cellular and molecular biology, biochemistry, nanotechnology, pharmacology, and immunology. Although demanding, with the numerous novel, promising and creative advancements that are revealing by valuable preclinical application, the challenges encounter the field of RNA therapeutics will finally be overcomed in the near future.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424. Erratum in: CA Cancer J Clin 2020;70:313.
2. Amini MA, Talebi SS, Karimi J. Reactive oxygen species modulator 1 (ROMO1), a new potential target for cancer diagnosis and treatment. Chonnam Med J 2019;55:136-43.
3. Amini MA, Karimi J, Talebi SS, Piri H. The association of COVID-19 and reactive oxygen species modulator 1 (ROMO1) with oxidative stress. Chonnam Med J 2022;58:1-5.
4. Amini MA, Karimi M, Talebi SS, Piri H, Karimi J. COVID-19 possibly deteriorates the conditions of cancer patients by increasing oxidative stress. Turk J Oncol 2022;37:361-9.
5. Lenkala D, LaCroix B, Gamazon ER, Geeleher P, Im HK, Huang RS. The impact of microRNA expression on cellular proliferation. Hum Genet 2014;133:931-8.
6. Ivey KN, Srivastava D. microRNAs as developmental regulators. Cold Spring Harb Perspect Biol 2015;7:a008144.
7. Winkle M, El-Daly SM, Fabbri M, Calin GA. Noncoding RNA therapeutics - challenges and potential solutions. Nat Rev Drug Discov 2021;20:629-51.
8. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004;116:281-97.
9. Roush S, Slack FJ. The let-7 family of microRNAs. Trends Cell Biol 2008;18:505-16.
10. Saliminejad K, Khorram Khorshid HR, Soleymani Fard S, Ghaffari SH. An overview of microRNAs: biology, functions, therapeutics, and analysis methods. J Cell Physiol 2019;234:5451-65.
11. Kalla R, Ventham NT, Kennedy NA, Quintana JF, Nimmo ER, Buck AH, et al. MicroRNAs: new players in IBD. Gut 2015;64: 504-17. Erratum in: Gut 2015;64:1008.
12. Hammond SM. An overview of microRNAs. Adv Drug Deliv Rev 2015;87:3-14.
13. Ha M, Kim VN. Regulation of microRNA biogenesis. Nat Rev Mol Cell Biol 2014;15:509-24.
14. Turchinovich A, Tonevitsky AG, Burwinkel B. Extracellular miRNA: a collision of two paradigms. Trends Biochem Sci 2016; 41:883-92.
15. Petrovic N, Ergun S. miRNAs as potential treatment targets and treatment options in cancer. Mol Diagn Ther 2018;22:157-68.
16. Cui M, Wang H, Yao X, Zhang D, Xie Y, Cui R, et al. Circulating microRNAs in cancer: potential and challenge. Front Genet 2019;10:626.
17. Seo J, Jin D, Choi CH, Lee H. Integration of microRNA, mRNA, and protein expression data for the identification of cancer-related microRNAs. PLoS One 2017;12:e0168412.
18. Kibel AS. Commentary on Circulating microRNAs as stable blood-based markers for cancer detection: Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, Peterson A, Noteboom J, O'Briant KC, Allen A, Lin DW, Urban N, Drescher CW, Knudsen, Stirewalt DL, Gentleman R, Vessella RL, Nelson PS, Martin DB, Tewari M, Divisions of Human Biology, Clinical Research, and Public Health Services, Fred Hutchinson Cancer Research Center, Seattle, WA. Urol Oncol 2009;27:461.
19. Calin GA, Cimmino A, Fabbri M, Ferracin M, Wojcik SE, Shimizu M, et al. MiR-15a and miR-16-1 cluster functions in human leukemia. Proc Natl Acad Sci U S A 2008;105:5166-71.
20. Cimmino A, Calin GA, Fabbri M, Iorio MV, Ferracin M, Shimizu M, et al. miR-15 and miR-16 induce apoptosis by targeting BCL2. Proc Natl Acad Sci U S A 2005;102:13944-9. Erratum in: Proc Natl Acad Sci U S A 2006;103:2464.
21. Li L, Li X, Zhu Y, Li L, Wu Y, Ying J, et al. Human trophoblast cell-derived extracellular vesicles facilitate preeclampsia by transmitting miR-1273d, miR-4492, and miR-4417 to target HLA-G. Reprod Sci 2022;29:2685-96.
22. Chen Z, Zhang M, Lu Y, Ding T, Liu Z, Liu Y, et al. Overexpressed lncRNA FTX promotes the cell viability, proliferation, migration and invasion of renal cell carcinoma via FTX/miR-4429/UBE2C axis. Oncol Rep 2022;48:163.
23. Liu J, Xie J, Xu E, Xu B, Zhou J, Zhou J, et al. CircRNA hsa_circ_0000043 acts as a miR-4492 sponge to promote lung cancer progression via BDNF and STAT3 expression regulation in anti-benzo[a]pyrene-trans-7,8-dihydrodiol-9,10-epoxide-transformed 16HBE cells. Toxicol Sci 2023;195:87-102.
24. Jin Y, Chen Z, Liu X, Zhou X. Evaluating the microRNA targeting sites by luciferase reporter gene assay. Methods Mol Biol 2013; 936:117-27.
25. Panda AC, Sahu I, Kulkarni SD, Martindale JL, Abdelmohsen K, Vindu A, et al. miR-196b-mediated translation regulation of mouse insulin2 via the 5'UTR. PLoS One 2014;9:e101084.
26. Goldoni D, Yarham JM, McGahon MK, O'Connor A, Guduric-Fuchs J, Edgar K, et al. A novel dual-fluorescence strategy for functionally validating microRNA targets in 3' untranslated regions: regulation of the inward rectifier potassium channel K(ir)2.1 by miR-212. Biochem J 2012;448:103-13.
27. Bierhoff H. Analysis of lncRNA-protein interactions by RNA-protein pull-down assays and RNA immunoprecipitation (RIP). Methods Mol Biol 2018;1686:241-50.
28. Singh S, Shyamal S, Panda AC. Detecting RNA-RNA interactome. Wiley Interdiscip Rev RNA 2022;13:e1715.
29. Sen R, Ghosal S, Das S, Balti S, Chakrabarti J. Competing endogenous RNA: the key to posttranscriptional regulation. Scientific WorldJournal 2014;2014:896206.
30. Cheng DL, Xiang YY, Ji LJ, Lu XJ. Competing endogenous RNA interplay in cancer: mechanism, methodology, and perspectives. Tumour Biol 2015;36:479-88.
31. Gao J, Liu F, Zhao X, Zhang P. Long non-coding RNA FOXD2-AS1 promotes proliferation, migration and invasion of ovarian cancer cells via regulating the expression of miR-4492. Exp Ther Med 2021;21:307.
32. Hu Q, Tai S, Wang J. Oncogenicity of lncRNA FOXD2-AS1 and its molecular mechanisms in human cancers. Pathol Res Pract 2019;215:843-8.
33. An Q, Zhou L, Xu N. Long noncoding RNA FOXD2-AS1 accelerates the gemcitabine-resistance of bladder cancer by sponging miR-143. Biomed Pharmacother 2018;103:415-20.

34. Yang X, Duan B, Zhou X. Long non-coding RNA FOXD2-AS1 functions as a tumor promoter in colorectal cancer by regulating EMT and Notch signaling pathway. Eur Rev Med Pharmacol Sci 2017;21:3586-91.
35. Bao J, Zhou C, Zhang J, Mo J, Ye Q, He J, et al. Upregulation of the long noncoding RNA FOXD2-AS1 predicts poor prognosis in esophageal squamous cell carcinoma. Cancer Biomark 2018;21: 527-33.
36. Zhang Y, Hu J, Zhou W, Gao H. LncRNA FOXD2-AS1 accelerates the papillary thyroid cancer progression through regulating the miR-485-5p/KLK7 axis. J Cell Biochem 2019;120:7952-61.
37. Liu X, Fu Q, Li S, Liang N, Li F, Li C, et al. LncRNA FOXD2-AS1 functions as a competing endogenous RNA to regulate TERT expression by sponging miR-7-5p in thyroid cancer. Front Endocrinol (Lausanne) 2019;10:207.
38. Wang A, Jin C, Li H, Qin Q, Li L. LncRNA ADAMTS9-AS2 regulates ovarian cancer progression by targeting miR-182-5p/FOXF2 signaling pathway. Int J Biol Macromol 2018;120(Pt B):1705-13.
39. Li W, Chen Y, Nie X. Regulatory mechanisms of lncRNAs and their target gene signaling pathways in laryngeal squamous cell carcinoma. Front Pharmacol 2020;11:1140.
40. Zhou B, Yuan W, Li X. Long intergenic noncoding RNA 319 (linc00319) promotes cell proliferation and invasion in lung cancer cells by directly downregulating the tumor suppressor MiR-32. Oncol Res 2017. doi: 10.3727/096504017X15016337254650 [Epub ahead of print]
41. Du W, Feng Z, Sun Q. LncRNA LINC00319 accelerates ovarian cancer progression through miR-423-5p/NACC1 pathway. Biochem Biophys Res Commun 2018;507:198-202.
42. Li F, Liao J, Duan X, He Y, Liao Y. Upregulation of LINC00319 indicates a poor prognosis and promotes cell proliferation and invasion in cutaneous squamous cell carcinoma. J Cell Biochem 2018;119:10393-405.
43. Zou J, Wu K, Lin C, Jie ZG. LINC00319 acts as a *microRNA-335-5p* sponge to accelerate tumor growth and metastasis in gastric cancer by upregulating *ADCY3*. Am J Physiol Gastrointest Liver Physiol 2020;318:G10-22.
44. Yang Y, Zhang F, Huang H, Xie Z, Huang W, Xie H, et al. Long noncoding RNA LINC00319 regulates ROMO1 expression and promotes bladder cancer progression via miR-4492/ROMO1 axis. J Cell Physiol 2020;235:3768-75.
45. Kim HJ, Jo MJ, Kim BR, Kim JL, Jeong YA, Na YJ, et al. Overexpression of Romo1 is an unfavorable prognostic biomarker and a predictor of lymphatic metastasis in non-small cell lung cancer patients. Onco Targets Ther 2018;11:4233-46.
46. Amini MA, Karimi J, Khodadadi I, Tavilani H, Talebi SS, Afshar B. Overexpression of ROMO1 and OMA1 are potentially biomarkers and predict unfavorable prognosis in gastric cancer. J Gastrointest Cancer 2020;51:939-46.
47. Kim HJ, Jo MJ, Kim BR, Kim JL, Jeong YA, Na YJ, et al. Reactive oxygen species modulator-1 (Romo1) predicts unfavorable prognosis in colorectal cancer patients. PLoS One 2017;12:e0176834.
48. Zhang PF, Wu J, Luo JH, Li KS, Wang F, Huang W, et al. SNHG22 overexpression indicates poor prognosis and induces chemotherapy resistance via the miR-2467/Gal-1 signaling pathway in epithelial ovarian carcinoma. Aging (Albany NY) 2019;11:8204-16.
49. Mao X, Ji T, Liu A, Weng Y. ELK4-mediated lncRNA SNHG22 promotes gastric cancer progression through interacting with EZH2 and regulating miR-200c-3p/Notch1 axis. Cell Death Dis 2021;12:957.
50. Zheng HL, Yang RZ, Xu WN, Liu T, Chen PB, Zheng XF, et al. Characterization of LncRNA SNHG22 as a protector of NKIRAS2 through miR-4492 binding in osteosarcoma. Aging (Albany NY) 2020;12:18571-87.
51. Fenwick C, Na SY, Voll RE, Zhong H, Im SY, Lee JW, et al. A subclass of Ras proteins that regulate the degradation of IkappaB. Science 2000;287:869-73.
52. Lu SR, Li Q, Lu JL, Liu C, Xu X, Li JZ. Long non-coding RNA LINC01503 promotes colorectal cancer cell proliferation and invasion by regulating miR-4492/FOXK1 signaling. Exp Ther Med 2018;16:4879-85.
53. Guo Y, Sun P, Guo W, Dong Z. Long non-coding RNA LINC01503 promotes gastric cardia adenocarcinoma progression via miR-133a-5p/VIM axis and EMT process. Dig Dis Sci 2021;66:3391-403.
54. Wang H, Sheng ZG, Dai LZ. Long non-coding RNA LINC01503 predicts worse prognosis in glioma and promotes tumorigenesis and progression through activation of Wnt/β-catenin signaling. Eur Rev Med Pharmacol Sci 2019;23:1600-9.
55. Pratama MY, Visintin A, Crocè LS, Tiribelli C, Pascut D. Circulatory miRNA as a biomarker for therapy response and disease-free survival in hepatocellular carcinoma. Cancers (Basel) 2020;12:2810.
56. Boo L, Ho WY, Ali NM, Yeap SK, Ky H, Chan KG, et al. MiRNA transcriptome profiling of spheroid-enriched cells with cancer stem cell properties in human breast MCF-7 cell line. Int J Biol Sci 2016;12:427-45.
57. Ahn SH, Ahn JH, Ryu DR, Lee J, Cho MS, Choi YH. Effect of necrosis on the miRNA-mRNA regulatory network in CRT-MG human astroglioma cells. Cancer Res Treat 2018;50:382-97.