ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY

ISSN: 1507-1367

e-ISSN: 2083-4640

Host gene and its guest: short story about relation of long-noncoding MIR31HG transcript and microRNA miR-31

Authors: Tomasz Kolenda, Anna Paszkowska, Alicja Braska, Joanna Kozłowska-Masłoń, Kacper Guglas, Paulina Poter, Piotr Wojtczak, Renata Bliźniak, Katarzyna Lamperska, Anna Teresiak

DOI: 10.5603/RPOR.a2023.0006

Article type: Review paper

Published online: 2023-02-01

This article has been peer reviewed and published immediately upon acceptance.
It is an open access article, which means that it can be downloaded, printed, and distributed freely, provided the work is properly cited.

Host gene and its guest: short story about relation of long-noncoding MIR31HG transcript and microRNA miR-31

10.5603/RPOR.a2023.0006

Tomasz Kolenda[1], Anna Paszkowska[1–3], Alicja Braska[2], Joanna Kozłowska-Masłoń[1–3], Kacper Guglas[4], Paulina Poter[5], Piotr Wojtczak[6], Renata Bliźniak[1], Katarzyna Lamperska[1, 2], Anna Teresiak[1, 2]

[1]*Laboratory of Cancer Genetics, Greater Poland Cancer Centre, Poznan, Poland*
[2]*Research and Implementation Unit, Greater Poland Cancer Centre, Poznan, Poland*
[3]*Faculty of Biology, Adam Mickiewicz University, Poznan, Poland*
[4]*1st Surgical Oncology and General Surgery Department, Greater Poland Cancer Centre, Poznan, Poland*
[5]*Department of Oncologic Pathology and Prophylaxis, Greater Poland Cancer Centre, Poznan, Poland*
[6]*Doctoral Studies, Medical University of Lodz, Lodz, Poland*

Correspondence to: Tomasz Kolenda, 1Greater Poland Cancer Centre, Laboratory of Cancer Genetics, Garbary 15, 61–866 Poznan, Poland; e-mail: kolenda.tomek@gmail.com

Abstract

Epigenetics is the changes in a cellular phenotype without changes in the genotype. This term is not limited only to the modification of chromatin and DNA but also relates to some RNAs, like non-coding RNAs (ncRNAs), both short and long RNAs (lncRNAs) acting as molecular modifiers. Mobile RNAs, as a free form or encapsulated in exosomes, can regulate neighboring cells or be placed in distant locations. It underlines the vast capacity of ncRNAs as epigenetic elements of transmission information and message of life.

One of the amazing phenomena is long non-coding microRNA-host-genes (lnc-MIRHGs) whose processed transcripts function as lncRNAs and also as short RNAs named microRNAs (miRNAs). MIR31HG functions as a modulator of important biological and cellular processes including cell proliferation, apoptosis, cell cycle regulation, EMT process, metastasis, angiogenesis, hypoxia, senescence, and inflammation. However, in most cases,

the role of MIR31HG is documented only by one study and there is a lack of exact description of molecular pathways implicated in these processes, and for some of them, such as response to irradiation, no studies have been done.
In this review, MIR31HG, as an example of lnc-MIRHGs, was described in the context of its known function and its potential uses as a biomarker in oncology.
Key words: microRNA; epigenetic; cancer biomarker

Long non-coding RNAs are important players in cellular function

The word epigenetics for most is the synonym for changes in the chromatin structure and DNA. However, it has changed in the last decades, and new elements of cellular control in response to physiological or pathological signals have transformed our knowledge considering epigenetics. Now, in the "modern era of epigenetic research", we look not only at the chromatin and DNA state but also, which seems more fascinating, the action of various molecular regulators, such as non-coding RNA (ncRNA) [1] (Fig. 1). ncRNAs consist of constitutive RNAs: tRNA, rRNA, snRNA, snoRNA, and a group of regulatory RNAs: siRNA, piRNA, miRNA, NAT, circRNA, and lncRNA [2–4]. Though long non-coding RNAs (lncRNAs) are not translated into proteins, they become over time valuable and significant molecules. The lncRNAs consist of over 200 nucleotides and their activity enables them not only to interact with proteins and other RNAs but also to regulate gene transcription and expression through changes in the structure of chromatin [5, 6]. Specified types of lncRNAs play a role in signaling, decoying, guiding, and building scaffolds for proteins and other RNA molecules [7].

Fragments encoding lncRNAs can occupy intergenic or intragenic positions. Specific intragenic genes can be located in intron, enhancer, promoter, or 3'UTR flanking regions [5, 6]. Here, it is important to mention that the lncRNAs of interest are closely related to genes that are encoded in the vicinity of the paired mRNA, resulting in their interaction with each other. lncRNAs appear to play an important role in the regulation of gene transcription in the nucleus or subsequent post-transcriptional modifications in the cytoplasm. Despite the opportunities afforded by lncRNA research, many difficulties are still encountered in fully understanding them due to their location in the genome. It should be noted that more than 50% of lncRNAs are long intergenic non-coding RNAs (lincRNAs) with no annotated proteins but some short peptides can also be found [8]. The direction of transcription and the

distance at which the transcript responsible for encoding protein is located from the lncRNA lead to the division of this group of RNAs into four classes: i) located on the same strand, ii) convergent, iii) divergent, and iv) isolated, which are located at least 50 kb from the closest protein-coding gene [15]. The main challenges in understanding the mechanisms of lncRNAs behavior are caused by different expression levels depending on tissue localization [10], frequent heterogeneity of isoforms, and numerous repeats in transcriptional initiation regions [11]. Moreover, as lncRNAs have been shown to vary with different expression levels, the specificity of their function in different cell types changes [12]. As it emerged, dysfunction of the activity or cellular mechanisms of lncRNAs may appear through pathological states including tumor progression through influence not only on the chromatin structure but also on several transcription factors [13]. According to GENCODE, NCBI Refseq, LNCipedia, and NONCODE number of lncRNAs' genes is estimated between 56'946 to 17'952 locus which gives 27'381 to 172'216 transcripts [14–17]. It is proven that aberration of both coding and non-coding RNAs play a crucial role in cancer biology [18]. lncRNAs regulate cell growth, cell cycle, cell phenotype, migration and invasion ability, and apoptosis [7]. The functions and activity of lncRNAs are still being investigated. More and more new elements are added, such as the possibility of interaction of lncRNAs with RNAi molecules, for example *UCA1*, *CASC2*, *GAS5*, *FER1L4*, *WDFY3-AS2*, *TP53TG1*, *FENDRR* or *SNHG1* lncRNAs with *miR-18a* [19]. What is more interesting, lncRNAs, such as *MIR31HG*, can be host genes for miRNAs and play a dual role as lncRNA and as a primary-miRNA transcript.

MIR31HG is a member of long non-coding microRNA-host-genes

MIR31 host gene (*MIR31HG*) belongs to a group of long non-coding microRNA-host-genes (lnc-MIRHGs) distinguished from lncRNAs due to coding the microRNA gene and transcript. *MIR31HG* functions in two specified RNA forms, as a long transcript, lncRNA, and as a host gene, which under processing is changed into a short non-coding RNA molecule, microRNA named *miR-31*. Dhir et al. estimated the distribution of miRNA between lncRNA and protein-coding genes and it is 82.5% and 17.5%, respectively. These lncRNAs can be divided into lincRNA (57.1%), pseudogene (13.2%), antisense (16.0%), and other (19.0%) types of transcripts. Moreover, these lncRNAs are the source of about 17.5% of miRNAs in humans [20].

It should be noted that lnc-MIRHGs are an under-studied class of lncRNAs in contrast to the well-known microRNAs which are hosted by them [21].

It is worth mentioning that miRNAs are transcribed as pri-miRNAs whose structure includes a terminal loop, stem, and 50 and 30 single-stranded overhangs at the ends. According to miRbase and GENCODE, there are 1’917 human miRNA genes, 1’917 hairpin precursors, and 2’654 mature sequences, and 1’881 miRNA genes [22]. Pri-miRNA does not perform the gene silencing function, so it is post-transcribed through canonical or non-canonical miRNA biogenesis pathways [23]. miRNAs, concerning their relationship with MIRHGs, can be categorized into: i) intronic, ii) exonic, ii) exon-intron junction (SO-miRNAs), and iv) intergenic miRNAs. These localizations in the gene and genome influence their biogenesis [21]. There are two main proposed biogenesis models of MIRHG and its intragenic miRNA: i) synergetic model which includes mirtron processing, cooperative of the splicing machinery and microprocessor, and a splicing-independent manner of miRNA production with the presence of splicing factors, and the second model, ii) competition model where miRNA production is alternative- and non-alternative-splicing-mediated. A detailed description of these two models is presented by Sun et al. [21]. It was shown that there is a correlation in expression between the miRNA and the corresponding MIRHG. Moreover, miRNA molecules, which are usually located within 50 kb, are derived from a single transcript. When miRNAs originate from an intron region, their expression is often correlated with MIRHG expression [26]. It should be noted that the expression of MIRHG can be regulated by tumor cells, more specifically by the promoters. The changes in methylation of the above promoters result in an altered expression of the encoded miRNA [27]. Moreover, in the case of intragenic miRNAs and their host, a negative feedback loop can be created which regulates the level of both transcripts [21]. It is worth noting that the expression of miRNA and MIRHG pairs is not always related in this way, but in some cases, it offers great diagnostic possibilities [27].

The function of MIRHGs as lncRNA transcripts alone is dicussive and some evidence indicates that they function as primary transcripts of miRNAs. On the other hand, some authors show the miRNA-independent role of lnc-MIRHGs such as *MIR22HG*, *MIR100HG*, *MIR205HG/LEADeR*, *RMST*, *CYTOR*, *LINC01138*, *LINC-PINT*, *MIR503HG*, *NEAT1*, *PVT1*, *H19* or *MIR222HG*, which are fully described by Sun et al. [25]. MIRHGs can be categorized as oncogenes or tumor suppressors, but this function can be specific to the type of cancer. MIRHGs can: i) act as ceRNA elements, ii) interact with DNA elements, or iii) with proteins as well as vi) regulate the interaction with proteins [25]. All these capabilities and functions make them an astonishing group of RNA molecules. Therefore, in this review we will continue to focus on one of them, *MIR31HG*, presenting the current state of knowledge.

MIR31HG — localization in the genome and biogenesis

The *MIR31HG* molecule has been known in the past by names: *LOC554202*, *hsa-lnc-31,* or *lncHIFCAR*. It is localized on chromosome 9 and consists of 4 exons. The length of the whole *MIR31HG* is about 150–106 Kb [28, 29]. According to GeneCards The Human Gene Database, the latest assembly of genomic locations shows that *MIR31HG* Gene is situated on the minus strand orientation on chr9:21’380’073-21’591’766 (GRCh38/hg38) and its size is estimated as 211’694 bases [29]. Based on GeneHancer (GH) data, 3 different enhancers and 2 different promoter/enhancer regions were distinguished for the *miR31HG* gene, which creates regulatory elements and has the transcription factor binding sites such as: different TRIM, ZNF, MYC, STAT3, ZEB2, NANOG or EZH2 proteins [29].

MIR31HG is over 200 nucleotides long and it is transcribed by RNA polymerase II and the mature transcript is polyadenylated. Augoff et al. showed that the *MIR31HG* (*LOC554202*) transcript is 2’246 bp long and it does not encode any protein products [27]. Moreover, the *MIR31HG* gene does not encode any short peptides which could be produced by this type of transcript [29]. These features cause *MIR31HG* to be indisputably classified as a long non-coding RNA (lncRNA). However, *MIR31HG* belongs to the unique subtype of lncRNAs because, in the first intron of *MIR31HG*, it harbors a sequence of other type of ncRNA molecule which is classified as a short-noncoding RNA, named *miR-31*. It should be noted that this first intron contains a CpG island, which is responsible for the transcription regulation of both types of ncRNA molecules [27]. What is interesting, the *MIR31HG* transcript is not post-translationally modified and 32 different transcriptional variants are distinguished with a length between 287 and 10’980 bp. It should be noted that no orthologs or paralogs for *MIR31HG* have been identified up to date [29].

The expression level of *MIR31HG* is tissue-specific and according to the GENE NCBI, the highest expression is observed in normal tissue taken from the urinary bladder and the lowest in the pancreas, liver, and heart [28].

The biological function of MIR31HG

It is known that *MIR31HG* plays an important role in cellular processes whose disturbance causes cancerogenesis or increases the rate of this process. The most described, where *MIR31HG* is involved, are cell proliferation, cell cycle, invasiveness, EMT process as well as apoptosis. However, *MIR31HG* has also been described in the context of angiogenesis, hypoxia, senescence, or inflammation (Fig. 2).

Cell proliferation and cell cycle

One of the most characteristic biological functions linked with *MIR31HG* is its influence on cellular proliferation. Nie et al. were the first to observe that upregulation of *MIR31HG* caused lower cell proliferation of gastric cancer cells *in vitro* and *in vivo* and its knockdown caused a reversed effect partly by regulating *E2F1* and *p21* [30]. Similarly, in HNSCC (head and neck squamous cell carcinoma) cells the knockdown of *MIR31HG* affects proliferation, cell cycle arrest in G1 or S phase, and apoptosis. This effect was caused by decreasing expression of *HIF1A* and *CCND1,* and increasing *p21* on mRNA and protein levels [31]. However, the opposite effect was observed in the case of breast cancer, where silencing of *MIR31HG* expression inhibits the proliferative ability of the cells, and its function is linked with the *POLDIP2* expression level [32]. Similarly, in lung squamous cell carcinoma (LSCC), inhibition of *MIR31HG* causes reduced cell proliferation, but the molecular way was not clearly explained [33]. Another study showed that *MIR31HG* knockdown inhibits not only cancer cell migration but also colony formation and cell proliferation [34].

In addition to the tumors' model, also in the case of human periodontal ligament stem cells, the influence of of *MIR31HG* on proliferation was found. Methylation of the *MIR31HG* promoter induced by mechanical force causes reduced expression of *MIR31HG* and upregulation of *IL-6*, *DNMT1*, and *DNMT3B*. The changes in the stem cells' proliferation can be overcome by *DNMT1* and *DNMT3B* knockdown, which interact with the upstream region of the *MIR31HG* promoter and induce its expression [35].

Invasiveness and EMT process

The migration and invasive ability are also linked with *MIR31H*G. It caused higher invasiveness of breast cancer cells [32] as well as of lung cancer cells [33]. It was observed that in the case of non-small-cell lung carcinoma (NSCLC), reduction of *MIR31HG* expression was associated with the EMT process and manifested by reduction of Twist1 and Vimentin expression and upregulation of E-cadherin. Authors stated that *MIR31HG* causes changes in the Wnt/β-catenin signaling pathway by reduction of *GSK3β* and *β-catenin* and also its knockdown was linked with phosphorylation of *GSK3β* [33]. It should be noted that *MIR31HG*, depending on the cellular state, does not induce cancer cell invasion but promotes paracrine senescence [36]. The role of *MIR31HG* in the EMT process was also observed in osteosarcoma, where upregulation of *MIR31HG* caused down-regulation of *miR-361*. This effect was manifested by upregulation in the protein levels of *miR-361*'s target genes,

vascular endothelial growth factor (VEGF), forkhead box M1 (FOXM1), and Twist in in vitro model and patients samples, as well as by downregulation of E-cadherin observed in cell lines after upregulation of *MIR31HG* [37].

Apoptosis

Feng et al. based on nasopharyngeal carcinoma indicated that the knockdown of *MIR31HG* causes inhibition of apoptosis by negative regulation of the *PI3K/AKT* signaling pathway [38]. Moreover, based on U2OS and Saos-2 cell lines it was indicated that apoptosis could be regulated by the expression level of miR-361 and its targets, VEGF, FOXM1, and Twist, as well as by changes in anti-apoptosis of B-cell lymphoma 2 (BCL2) and cyclin D (CCND1) proteins levels whose expression was inhibited by artificial up-regulation of *MIR31HG* [37].

Inflammation

Gao et al.'s studies identified the elevation of *MIR31HG* in psoriatic skin. The expression of two types of keratin, *KRT6* and *KTR16*, was significantly up-regulated in keratinocytes from patients with psoriasis in comparison to normal samples, and *MIR31HG*-dependent. As mentioned before, also the cell cycle was changed after *MIR31HG* silencing in keratinocytes and it was shown that there were more keratinocytes in the G2/M phase relative to cells in the S phase, indicating that *MIR31HG* knockdown inhibits the proliferation of HaCaT keratinocytes. Moreover, it was indicated that stimulation of proinflammatory interleukin 17A (IL-17A), interleukin 22 (IL-22), tumor necrosis factor alpha (TNF-α), and interleukin 1 alpha (IL-1α) cytokines was able to elevate *MIR31HG* expression. It should be noted that *BAY*, *NF-κB* inhibitor, and *p65* regulations additionally showed that *NF-κB* activation has an impact on *MIR31HG* [39].

Senescence

Senescence can also be induced in the presence of oncogenes as a response aimed at tumor suppression, such a mechanism is called oncogene-induced senescence. A group of researchers has shown that *MIR31HG* is also involved in this induction [40]. Montes et al. based on cell models, showed that *MIR31HG* plays a dual role depending on the localization in cytoplasm and nucleus. *MIR31HG* is overexpressed and translocates to the cytoplasm during BRAF-induced senescence and by kinase RSK causes phosphorylation of YBX1.Finally, it changes the senescence-associated secretory phenotype (SASP) of cells by *IL1A* translation activation [41].

MIR31HG can be used as a biomarker

The potential role of *MIR31HG* as a biomarker was analyzed on both the Cancer Genome Atlas (TCGA) data and collected samples by specified research groups or cell lines. However, independent research about the same cancer type was done in only a few cases [33, 34, 42–53]. A growing number of studies indicate that *MIR31HG* plays an important role in cancer as an oncogene or as a suppressor. It was shown that *MIR31HG* is down-regulated in gastric cancer [30], bladder cancer [34, 42], hepatocellular carcinoma [57], pancreatic ductal adenocarcinoma [58], and glioblastoma [65]. Moreover, up-regulation of *MIR31HG* was indicated in the case of breast cancer [32], head and neck cancer cancers [31, 67, 68], melanoma [54], cervical carcinoma [56], osteosarcoma [57], non-small cell lung cancer [33, 43, 44], lung adenocarcinoma [44–47], colorectal cancer [48–51], thyroid cancer [52, 53], as well as papillary thyroid cancer [64]. It should be noted that two independent studies checking the role of *MIR31HG* in esophageal squamous cell carcinoma indicated opposite expression levels of this lncRNA [59, 60].

MIR31HG can be used as a diagnostic biomarker and it is detectable in tissue as well as in biological fluids such as plasma [31, 60]. Moreover, *MIR31HG* could describe the more invasive types of cancer, with advanced tumor–nodules–metastases (TNM) stages, lymph node invasion as well as distant metastasis [31, 32, 43, 54, 57, 59, 60, 62] and its higher expression is associated with worse disease-free and overall survival (OS). However, the opposite meaning of *MIR31HG* as a prognostic biomarker is observed in the case of bladder cancer [42], hepatocellular carcinoma [57], esophageal squamous cell carcinoma [59], and gastric cancer [30]. For these cancers, a higher expression level of *MIR31HG* is negatively correlated with more advanced TNM-stage [30, 42, 57], with lower tumor nodule number, vascular invasion [57], metastasis [57, 59] or poor tumor differentiation [59]. Analysis of patients' survival revealed that the higher expression levels of *MIR31HG* were associated with longer survival for these types of cancers [30, 57, 59].

In the end, it should be noted that Chang et al. indicated potential features of *MIR31HG* as a predictive biomarker, and higher levels of *MIR31HG* were associated with increased cisplatin resistance [55], but there is only one study exploring this problem. All studies and results describing *MIR31HG* as a biomarker are included in Table 1.

Table 1. MIR31 host gene (*MIR31HG*) as a potential biomarker in different types of cancers

Type of cancer	Methods of detection	Sample type	Type of biomarker	Description	Ref.

Head and neck cancer	qRT-PCR	60 paired normal and adjacent cancer samples; plasma; FaDu and Cal-27 cell lines	diagnostic, prognostic	Overexpressed in cancer tissue and plasma of the early and advanced stages of patients Correlated with advanced T-stages and lymph node invasion Lower level was associated with better OS and RFS *MIR31HG* regulated cell cycle progression and apoptosis by targeted *HIF1A* and *p21*	[31]
Melanoma	qRT-PCR	55 patients' tissues and Human Epidermal Melanocytes (cell line)	diagnostic, prognostic	Overexpressed in cancer tissue and cell lines Associated with lymph nodes invasion Distal metastasis and higher TNM-stages Lower *MIR31HG* expression was characteristic with lower malignancy by decreased cell proliferation, and migration and invasion rates	[54]
Breast cancer	qRT-PCR	50 paired normal and adjacent cancer samples and T47D, BT-474, SUM149-Luc, BT549, and MCF-10A cell lines	diagnostic, prognostic	Overexpressed in cancer tissue and cell lines Correlated with the patient's tumor diameter Correlated with tumor TNM-stages and lymph node metastasis Lower level associated with better survival *MIR31HG* influenced on proliferation, migration and invasion abilities by regulation of *POLDIP2*	[32]
Oral squamous cell carcinoma	TCGA (RNAseq); qRT-PCR	520 cancer and 44 normal TCGA samples; Cytobrushed samples and	diagnostic, prognostic and predictive	Overexpressed in cancer tissue and cell lines *MIR31HG* enhanced oncogenic phenotype especially by enrichment of *Wnt* pathway Lower level associated with better survival Correlated with higher proliferation and wound healing closure rates Higher *MIR31HG* associated with increased	[55]

		matched mucosa from 28 patients and OC3, OC4, OC5, SAS, OECM1, FaDu, and NOK cell lines		cisplatin resistance	
Cervical carcinoma	TCGA (RNAseq); qRT-PCR	24 normal and 104 lesions/cancer samples from GEO and 306 cancer and 13 normal TCGA data sets; 46 pairs of cervical cancer tissues and adjacent patients' tissues and CasKi, SiHa, C33A and HcerEpic cell lines	diagnostic, prognostic	Overexpressed in cancer tissue and cell lines, Knockdown of *MIR31HG* suppressed cell growth and invasion *MIR31HG* regulated *miR-361-3p* and through it modulated epithelial membrane protein 1 (*EMP1*) mRNA expression level	[56]

Osteosarcoma	qRT-PCR	40 paired normal and adjacent cancer samples patients' tissues and 143B, MG63, U2OS, Saos-2 and hFOB1.19 cell lines	diagnostic	Overexpressed in cancer tissue and cell lines Higher *MIR31HG* expression associated with higher tumor stages and distant metastasis *miR-361* was sponged by *MIR31HG* and down-regulated Knockdown of *MIR31HG* restored the expression of *miR-361* in cell lines *miR-361* induced cell apoptosis and G1/S arrest, inhibited proliferation and migration in Saos-2 and U2OS cells, and *MIR31HG* had reversed effect *MIR31HG* by regulation of *miR-361* targeted *VEGF*, *FOXM1* and *Twist*, and caused upregulation of *BCL2*, *CCND1* and EMT phenotype Higher level of VEGF, FOXM1 and Twist were positively correlated with MIR31HG in patients' samples *MIR31HG* promoted tumor growth by regulation of *miR-361* and *VEGF*, *FOXM1* and *Twist in vivo*	[57]
Bladder cancer	TCGA (RNAseq); qRT-PCR	102 FFPET patients' samples and 370 TCGA patients, and SCaBER, UMUC3, T24, RT112, RT4 and UROtsa cell lines	diagnostic, prognostic	Decreased in cancer tissue and cell lines and depended on the spliced variants (*MIR31HG*ΔE1 and *MIR31HG*ΔE3) *MIR31HG*ΔE3 highly expressed in the case of the basal subtype Higher expression of *MIR31HG*ΔE1 and *MIR31HG*ΔE3 associated with worse OS and DFS Knockdown of *MIR31HG* inhibited cell proliferation, colony formation, and migration abilities	[34]

Colorectal cancer	GEO and TCGA (Arrays/RNAseq); qRT-PCR	nearly 2000 CRC biopsies and preclinical models; patient-derived xenografts; cell lines	diagnostic, prognostic	Strongly correlated with *miR-31-5p* *MIR31HG* changed in 12% of patients and associated with depletion of CMS2-canonical subgroup and shorter RFS 5-year RFS for patients (stage II subgroup) with *MIR31HG* outlier status lower than those with normal-like expression *MIR31HG* outlier status associated with worse outcome in clinical high risk groups (CMS4-mesenchymal gene expression subtype) Patients with *MIR31HG* outlier expression had reduced expression of *MYC* targets, higher expression of epithelial-mesenchymal transition, *TNF-α/NFκB*, *TGF-β*, and *IFN-α/γ* gene expression signatures Prognostic value of *MIR31HG* outlier status was independent of cytotoxic T lymphocyte and fibroblast infiltration	[49]
Non-small cell lung cancer	qRT-PCR	88 paired normal and adjacent cancer samples patients' tissues and A549, H1299, NCIH460 and 16HBE cell lines	diagnostic, prognostic	Overexpressed in tumor tissues compared with adjacent normal tissues Higher *MIR31HG* expression associated with histological differentiation grade, lymph node metastasis and higher TNM-stages Higher *MIR31HG* expression associated with worse OS *MIR31HG* knockdown inhibited proliferation and invasion abilities Lower expression suppressed the EMT phenotype (reduced *Twist1* and *Vimentin*, and increased *E-cadherin* expressions) Inhibition of the *Wnt/β-catenin* signaling pathway (reduced expression of *GSK3β* and *β-catenin*, and increased phosphorylation of (p)-GSK3β)	[33]

Lung adenocarcinoma	qRT-PCR	132 patients' tissues and 20 adjacent non-cancerous samples, and A549, H2228, H1975, H1299 and BEAS-2B cell lines	diagnostic, prognostic	Overexpressed in cancer tissues and cell lines Associated with higher TNM-stages and differentiated degree Higher *MIR31HG* was an independent unfavorable OS factor Knockdown *MIR31HG* caused inhibition of cells proliferation and blocked cell-cycle and didn't changed cell apoptosis No correlation between *MIR31HG* and *miR-31* expressions and knockdown of *MIR31HG* had no effect on the *miR-31* level	[45]
Non-small cell lung cancer	qRT-PCR	50 paired normal and adjacent cancer patients' tissues and H1299, A549, H1975, H460 and BEAS-2B cell lines	diagnostic, prognostic	Overexpressed in tumor tissues and cell lines SP1, transcription factor, binds to promoter region of *MIR31HG* and induces its expression Higher *MIR31HG* was an independent predictor worse OS *MIR31HG* associated with less differentiation degree and higher TNM-stages Knockdown of *MIR31HG* inhibited migration, invasion and metastasis abilities, Overexpression of *MIR31HG* reduced the expression of *miR-214* and induced cancer progression	[43]
Colorectal cancer	qRT-PCR	30 paired normal and adjacent cancer patients' tissues and RKO, SW480, SW620,	diagnostic, prognostic	Overexpressed in tumor tissues and cell lines Associated with worse prognosis Overexpression of *MIR31HG* induced proliferation, growth, invasion, glycolysis and lung metastasis and angiogenesis observed *in vitro* and *in vivo* *MIR3HG* upregulated higher expression of *YY1* (mRNA and protein) Forced overexpression of *YY1* induced	[50]

		LoVo and HCT116 cell lines		overexpression of enhanced *MIR31HG* *MIR31HG* inhibits *miR-361-3p* which has and anti-tumor effect by targeting *YY1*	
Bladder cancer	qRT-PCR	55 paired normal and adjacent cancer patients' tissues and T24, 5637, UM-UC-3, SW780 and SV-HUC-1 cell lines	diagnostic	Downregulated in tumor tissues and cell lines *MIR31HG* negatively associated with TNM-stages	[42]
Thyroid cancer	qRT-PCR	29 paired normal and adjacent cancer patients' tissues and SW579, TPC-1, HTH83 and Nthy-ori 3–1 cell lines	diagnostic, prognostic	Overexpressed in tumor tissues and cell lines Higher *MIR30HG* associated with worse prognosis Knockdown of *MIR30HG* reduced proliferation, invasion, migration, promoted cell apoptosis *in vitro* and tumor growth *in vivo* *MIR30HG* regulated the expression of *miR-761* which in turn regulates *MAPK1*	[52]
Hepatocellular carcinoma	qRT-PCR	42 paired normal and adjacent cancer patients' tissues and SMMC7721, HepG2,	diagnostic, prognostic	Downregulated in tumor tissues and cell lines Higher expression associated with better OS Higher expression correlated with lower tumor nodule number, lower vascular invasion and lower TNM-stages Overexpression of *MIR31HG* reduced proliferation and metastasis *in vitro* and *in vivo* *MIR31HG* regulates *miR-575* expression, which	[57]

		Huh7, SK-hep1 and 293 T (HEK) cell lines		has oncogenic properties, and influences on its target — *ST7L* There was a reciprocal inhibition between *MIR31HG* and *miR-575* in the same RISC complex	
Pancreatic ductal adenocarcinoma	GEO (Array); qRT-PCR	GEO 45 paired normal and adjacent cancer patients' tissues and AsPC-1, PANC-1, CFPAC-1, Hs 766 T, SW 1990, MIA PaCa-2, BxPC-3 and hTERT-HPNE cell lines	diagnostic	Overexpressed in tumor tissues and cell lines Knockdown of *MIR31HG* reduced cell growth, induced apoptosis and G1/S arrest, and inhibited invasion *in vitro* as well as tumor growth *in vivo* *miR-193b* targets *MIR31HG* and they have inverse correlation *MIR31HG* may act as an endogenous “sponge” by regulation of *miR-193b* and its' targets (*CCND1*, *Mcl-1*, *NT5E*, *KRAS*, *uPA*, and *ETS1*)	[58]
Esophageal squamous cell carcinoma	qRT-PCR	185 paired normal and adjacent cancer patients' tissues	diagnostic, prognostic	Downregulated in tumor tissues and cell lines Lower expression *MIR31HG* associated with poor differentiation, advanced lymph node metastasis positive distant metastasis and higher TNM-stages, Higher expression of *MIR31HG* associated with better OS and it is an independent prognostic marker for survival	[59]

Esophageal squamous cell carcinoma	qRT-PCR	53 paired normal and adjacent cancer patients' tissues, 53 plasma samples from patients and 39 from healthy donors, and EC9706, EC1 and Het-1A cell lines	diagnostic, prognostic	Overexpressed in tumor tissues, plasma and cell lines Expression level of *MIR31HG* in tissue and plasma from the same patient was positively correlated Higher expression observed in tissue and plasma samples of patients with higher TNM-stages and positive lymph node metastases *MIR31HG* displayed high diagnostic sensitivity and specificity for predicting cancer occurrence Knockdown of *MIR31HG* reduced proliferation, migration, and invasion abilities Reduction of *MIR31HG* caused inhibition of *Furin* and *MMP1*	[60]
Gastric cancer	qRT-PCR	42 paired normal and adjacent cancer patients' tissues and SGC7901, BGC823, MGC803, MKN45 and GES-1cell lines	diagnostic, prognostic	Downregulated in tumor tissues and cell lines Associated with larger tumor size and advanced pathological stages Lower *MIR31HG* expression associated with worse PFS and OS Overexpression of *MIR31HG* inhibited cell proliferation *in vitro* and tumor growth *in vivo* Knockdown of *MIR31HG* promoted cell proliferation partly via regulation of *E2F1* and *p21* expressions	[30]
Oral squamous cell	GEO (array) qRT-PCR	GEO 22 normal and 57 cancer patients'	diagnostic, prognostic	Overexpressed in tumor tissues Higher level of *MIR31HG* associated with worse OS and RFS (independent prognostic predictor) Overexpression of *MIR31HG* induced pseudo-	[61]

carcinoma		tissues, 15 paired normal and adjacent cancer patients' tissues and SAS cell line		hypoxic phenotype Knockdown of *MIR31HG* reduced hypoxia-induced *HIF-1α* transactivation, sphere-forming ability, metabolic shift and metastatic potential *in vitro* and *in vivo* *MIR31HG* directly bound and facilitated the recruitment of *HIF-1α* and *p300* cofactor to the target promoters	
Ovarian cancer	TCGA (RNAseq), qRT-PCR	352 TCGA patients' cancer tissues, and TOV-21G, A2780, SKOV3, and IOSE80 cell lines	diagnostic, prognostic	*MIR31HG* and other lncRNAs (*ACTA2-AS1, CARD8-AS1, HCP5, HHIP-AS1, HOTAIRM1, ITGB2-AS1, LINC00324, LINC00605, LINC01503, LINC01547, MIR155HG, OTUD6B-AS1, PSMG3-AS1, SH3PXD2A-AS1*, and *ZBED5-AS1*) associated with OS Those lncRNAs correlated with patient age at initial pathologic diagnosis, lymphatic invasion, tissues source site, and vascular invasion	[62]
Colon Cancer	TCGA (RNAseq)	166 TCGA stage II colon cancer patients	diagnostic, prognostic	*MIR31HG* as well as *WASIR2*, *miR-200a* and *miR-155* overexpressed in cancer tissue Lower *MIR31HG* expression associated with better OS 4 lncRNA-miRNA signature can be used as independent prognostic value of OS for stage II colon cancer with high sensitivity and specificity Correlated genes with *MIR31HG* were associated with the EMT process and the *VEGFR3* signaling in lymphatic endothelium pathways	[63]
Colorectal Cancer	TCGA (RNAseq), qRT-PCR	TCGA 593 tumor and 51 paired normal and adjacent cancer	diagnostic, prognostic	*MIR31HG* as well as *LINC00461, LINC01055, ELFN1-AS1, LMO7-AS1, CYP4A22-AS1, AC079612.1, LINC01351* associated with OS Risk factors for the prognosis with high sensitivity and specificity The index based on the 7 survival-related IRLs	[51]

		patients' tissues		were accurate in the prognosis monitoring IRLs index were correlated with a tumor status and N-stage and immune cell infiltration of CD4+ T cells and dendritic cells	
Papillary thyroid cancer	GEO (array) qRT-PCR	GEO 136 normal and 157 cancer patients' tissues, 50 paired normal and adjacent cancer patients' tissues	diagnostic	Five upregulated (*ENTPD1*, *THRSP*, *KLK10*, *ADAMTS9*, *MIR31HG*) and five downregulated (*SCARA5*, *EPHB1*, *CHRDL1*, *LOC440934*, *FOXP2*) genes For this ten genes the most highly enriched GEO terms were: extracellular exosome, cell adhesion, positive regulation of gene expression, ECM organization, tyrosine metabolism, complement and coagulation cascades, CAMs, transcriptional misregulation and *ECM*-receptor interaction pathways	[64]
Lung adenocarcinoma	TCGA (RNAseq), qRT-PCR	TCGA 465 tumor and 43 paired normal and adjacent cancer patients' tissues	diagnostic, prognostic	*MIR31HG* , *CEBPA-AS1*, *GVINP1* and *RAET1K* were selected after Cox analysis and OS prognostic gene signature was developed with high sensitivity and specificity *MIR31HG* significantly associated with survival rate, Four-lncRNA signature had prognostic value to predict tumor stage T stage, N stage, neoplasm cancer and primary therapy outcome 494 genes, which were coexpressed with lncRNAs of the risk score model, were associated with signal transduction, blood coagulation, pathways in cancer and chemokine signaling pathways	[47]
Glioblastoma	qRT-PCR		diagnostic, prognostic	*MIR31HG* deleted in over 73% of all GBMs *miR-31* status: 30.92% homozygous null, 42.68% heterozygous and 26.40% wildtype In low grade gliomas *MIR31HG* status: 6.96% homozygous null, 27.04% heterozygous, and 66% wild type	[65]

				Loss of one or both copies of *MIR31HG* significantly reduced the levels of *miR-31* Homozygous *MIR31HG* deletions predominantly associated with Mes- and C-GBMs *MIR31HG* deletions associated with shorter MMS (Median Months Survival) for patients with primary GBM and for patients with Mes-GBM *CDKN2A* deletions associated with diminished DFS times in all GBM, and patients with N-GBM but which lies adjacent to *MIR31HG*, did not predict shorter MMS in patients with Mes-GBM or primary GBM *MIR31HG* deletions not associated with diminished DFS *miR-31* inhibits *TRADD* and consequently *NF-κB* signaling and influencing on *MIR31HG* promoter containing three putative *NF-κB* binding sites	
Lung squamous cell carcinoma and lung adenocarcinoma	TCGA (RNAseq)	504 LUSC and 522 LUAD samples from TCGA	diagnostic, prognostic	*MIR31HG* is altered as deleted gene in 0.14 frequency in the case of LUAD *MIR31HG*, *CDKN2A-AS1* and *LINC01600* predicted poor OS in LUAD *MIR31HG* and *LINC01600* play their roles in female patients, while *CDKN2A-AS1* play its role in male patients Important molecular functions for both *CDKN2A-AS1* and *MIR31HG*-coexpressed genes were binding and catalytic activity — the top two enriched biological pathways were cellular process and metabolic process, and the most enriched pathway was the *P53* pathway; *IFNE*, *CDKN2A* and *MTAP* cBioPortal analysis results showed that all three coexpressed genes shared very similar alteration	[46]

				patterns with *CDKN2A-AS*1 and *MIR31HG* *MTAP* was the only gene located between *CDKN2A-AS1* and *MIR31HG*. *CDKN2A* was next to, and partially overlapped with, *CDKN2A-AS1*, and *IFNE* was located in the *MIR31HG* intron	
Colon Cancer	GEO and TCGA (Arrays/RNAseq)	1089 colon cancer patients from GEO and 391 patients from TCGA	diagnostic, prognostic	*MIR31HG*included in as one of the recurrence-associated six-lncRNAs (*LINC0184, AC105243.1, LOC101928168, ILF3-AS1*, and *AC006329.1*) Score model based on the six-lncRNA signature higher in the recurrent patients than non-recurrent patients lncRNA signatures effectively distinguish between high and low risk of cancer recurrence Only combination of six lncRNAs gives the greatest predictive ability (accuracy rate of 72.2% and AUC of 0.724) Six-lncRNA signature was independent of clinicopathological factors, has potential to differentiated patients, with similar clinical stage, into low and high risk subgroups Patients with higher expression level of these six lncRNAs displayed significantly higher recurrence risk status and RFS Functional analysis of the six lncRNA signature indicated implication of them into ATP metabolic processes, cell proliferation and angiogenesis, cell death, leukocyte differentiation	[66]
Thyroid Cancer	GEO and TCGA (Arrays/RNAseq),	57 PTC with a reference sample (pool of 9 adjacent normal	diagnostic, prognostic	Upregulated in patients' cancer samples Correlated with M and N stages and positive lymph nodes examined status *MIR31HG* overexpression correlated with high immune infiltrate levels of CD8+ T cells, macrophage, neutrophil, myeloid dendritic cells,	[53]

	qRT-PCR	thyroid tissue) and 4 PTC against 4 matched adjacent normal thyroid tissues from GEO and 391 patients from TCGA, CAL62 and SW579 cell lines		and B cells Knockdown of *MIR31HG* reduced cell proliferation and cycle progression *MIR31HG* associated with metabolic pathways, vesicle-mediated transport, tricarboxylic acid cycle, Hedgehog signaling pathway, and Hippo signaling pathway including *CCND2*, *CCND3*, *SDHC*, *SDHD*, *SUCLA2*, and *SUCLG1*	
Colorectal cancer	GEO and TCGA (Arrays/RNAseq)	TCGA 647 tumor and 51 paired normal and adjacent cancer patients' tissues and 122 patients's samples from GEO	diagnostic, prognostic	*MIR31HG* with other four lncRNAs (*H19*, *HOTAIR*, *WT1-AS*, and *LINC00488*) closely related to the OS Five-lncRNA signature was independent prognostic marker of the high-risk scores' patients which had poor survival rates High-risk score based on five-lncRNA signature associated with more advanced TNM stages and residual tumor In the univariate analysis risk score of the five-lncRNA model and some of clinical features (age, TNM stages, residual tumor) were associated with the OS In the multi-variate analysis, the five-lncRNA model displayed an independent prognostic factor Patient's prognosis separated by risk score and TNM staging were different: patients with lower risk score and tumor grade displayed better prognosis	[48]

				The risk score and clinicopathological features displayed better informative predict the patient’s 1, 3, 5-year survival Five-lncRNA model was associated with signaling pathway regulating pluripotency of stem cells, *WNT*, *Hippo* signaling path-way, basal cell carcinoma and colorectal cancer, negative regulation of translation, extracellular space, transcription from RNA polymerase II promoter, odontogenesis and negative regulation of fibroblast proliferation	
Oral squamous cell carcinoma	GEO (Arrays)	167 OSCCs and 45 oral mucosa from healthy controls from GEO and validation using 74 oral cavity squamous cell carcinoma and 29 adjacent normal tissue; GSE9844 with 26 tongue squamous cell	diagnostic	*MIR31HG* and 13 lncRNAs (*LOC441178*, *C5orf66-AS1*, *HCG22*, *FLG-AS1*, *CCL14/CCL15-CCL14*, *LOC100506990*, *TRIP10*, *PCBP1-AS1*, *LINC01315*, *LINC00478*, *COX10-AS1/LOC100506974*, *MLLT4-AS1*, and *DUXAP10/LINC01296*) were validated in all three datasets, and were upregulated Its expression differs between HPV-positive OPC and HPV-negative OPC, and is downregulated in *HPV* positive ones It is significantly differentially expressed between subsites of OSCC (OPC vs. OCC) *miR31HG* levels between smokers and non-smokers were indicated *miR31HG* was not validated by qRT-PCR in patients samples	[67]

		carcinoma and 12 matched adjacent normal tissue and GSE6791 comprised of 28 cervical cancers, 42 head and neck cancers and 14 site-matched normal oral tissue from GEO			
Lung squamous cell carcinoma and lung adenocarcinoma	TCGA (RNAseq)	TCGA 504 tumor and 46 paired normal and adjacent cancer patients' tissues	diagnostic, prognostic	3'366 mRNAs, 79 miRNAs and 151 lncRNAs were identified as involved in development of LUSC Only lncRNA *MIR99AHG* positively correlated with *OS* and *PLAU*, *miR-31-5p*, *miR-455-3p*, *FAM83A-AS1*, and *MIR31HG* were negatively associated with OS Only *PLAU* was validated using qRT-PCR and was upregulated in SK-MES-1 cells compared with 16-BBE-T cells Changed genes were associated with signal transduction, cell adhesion, blood coagulation, immune response, cell proliferation, apoptosis, transmembrane transport or small molecule metabolic processes	[44]

Laryngeal squamous cell carcinoma	Arrays and qRT-PCR	39 pairs of LSCC tissues and adjacent non-neoplastic tissues, microarray results deposit (GSE84957)	diagnostic, prognostic	1459 lncRNAs (846 up-and 613 down-regulated) and 238 mRNAs (1542 up- mRNAs and 839 down-regulated) were differentially expressed, *ITGB1*, *HIF1A*, and *DDIT4* were core mRNAs involved in matrix organization, cell cycle, adhesion, and metabolic pathway *MIR31HG* was positively correlated with *HIF1A* and *lncRNA NR_027340* was positively correlated with *ITGB1*	[68]

qRT-PCR — real-time quantitative reverse transcription polymerase chain reaction; RFS — relapse-free survival; OS — overall survival; TNM — tumor–nodules–metastases; TCGA — Cancer Genome Atlas; EMT — epithelial to mesenchymal transition; VEGF — vascular endothelial growth factor; FOXM1 — forkhead box M1; DF — disease-free survival; CMS — consensus molecular subtype; GSK3β — glycogen synthase kinase 3 beta; PFS — progression-free survival; lncRNAs — long RNAs; IRLs — immune-related lncRNAs; ECM — extracellular matrix; CAMs — cell adhesion molecules; Mes-GBM — mesenchymal glioblastoma; LUAD — Lung adenocarcinoma; LUSC — lung squamous cell carcinoma; AUC — area under the curve; ATP — adenosine triphosphate; PTC — papillary thyroid carcinoma; HPV — human papilloma virus; OSCC — oral cavity squamous cell carcinoma; OPC (oropharyngeal cancer; OCC (oral cavity cancer); LSCC — lung squamous cell carcinoma

"Small but crazy": miR-31

miR-31 is a short non-coding RNA, classified as microRNA (miRNA), and is the product of specific cleavage of *MIR31HG* transcript. miRNA molecules can be responsible for controlling many genes in a differentiated way [69, 70]. *miR-31* affects many processes not only in normally functioning cells, but is also important in disease and cancer processes. Based on results obtained from different tissues and cancer cell lines it was demonstrated that *miR-31* exhibits a whole spectrum of expression depending on tissue type. It is worth mentioning that the *miR-31* precursor was present in all tested cell lines but its mature form was predominantly found in tumor cell lines [71]. *miR-31* regulates cell proliferation by affecting the genes responsible for this process, such as *LATS1*, and *CREG*, in vascular smooth muscle cells [72, 73]. An excellent example is the mechanism studied in colon cancer

cells when *miR-31* overexpression targets *E2F2*, which acts as a tumor suppressor on colon cancer cell proliferation [74]. As for Ewing sarcoma, the effect of *miR-31* was identified as a tumor suppressor. In cell lines transfected with *miR-31*, there was a significant reduction in Ewing sarcoma cell proliferation, as well as increased apoptosis resulting in a decrease in tumor invasiveness [75]. The expression level of *miR-31* in cervical cancer, CIN, and normal uterine tissues was also examined. The results proved that the expression in cancer cells was elevated compared to non-tumor cells, and in addition, this phenomenon appeared to be associated with the occurrence of lymph node metastasis (LNM). It was demonstrated that such an effect increases cell proliferation, and cell migration, and thus invasiveness is also significantly increased, indicating that *miR-31* acts as an oncogene in this case [76]. In patients with non-small cell lung cancer (NSCLC), a relationship was discovered between the expression levels of *MIR31HG* and, consequently, *miR-31*, and the proliferation and clonogenic growth of tumor cells. The study showed that reducing their expression *in vitro* also reduces the growth of NSCLC cells, supporting the fact that *miR-31* had an oncogenic effect [77].

Moreover, *miR-31* plays an important role in the induction of senescence in breast cancer cells. Obtained results showed that overexpression of *miR-31* affected the repression of the polycomb group (PcG) protein BMI1, accompanied by the induction of cell aging. This offers the prospect of manipulating *miR-31* expression to control senescence and oncogenesis in breast cancer [78]. Few studies are based on healthy tissues and the effects on the aging of non-tumorigenic cells. For example, *miR-31* influences aging by regulation of dystrophin protein. Increased expression of *miR-31* resulted in direct inhibition of the translation of this protein which causes aging and damaged processes in muscle cells [79]. Capri et al. examined the miRNA expression levels to determine the age match between donor and recipient in the case of hepatocytes. It was indicated that *miR-31* is hyper-expressed in older donors, at levels up to 4.5 times higher than in younger individuals. Interestingly, these results were only noted in male patients, and female samples showed only a trend of increased expression with age [80]. Moreover, it was indicated in the case of endothelial cells (umbilical cord-derived), that the fold change of *miR-31* was one of the most upregulated miRNAs during the aging process [81].

It should be noted that *miR-31* regulates cell differentiation and has a role in determining cell fate. Li et al. investigated neural stem cells (NSCs) and the process of their differentiation into motor neurons (MNs) and correlated changes in *miR-31* expression with different states. Initial studies showed high levels of expression of this molecule in NSCs derived, for

example, from the spinal cord, while much lower levels in MNs. Comparison of the expression profiles led to the conclusion that high levels of *miR-31* have a stemness-maintaining effect in NSCs by inhibiting differentiation, especially in MNs [82]. Neuronal precursor cells (NPCs) appeared to be another cell in which *miR-31* plays a role in differentiation. It was shown that *Lin28*, *c-Myc*, *SOX2*, and *Oct4* act to inhibit the activity and expression of *miR-31*, consequently, impairing the process of NPC differentiation into astrocytes and astrocyte maturation itself in gliomas. As later analyses showed *miR-31* also downregulates selected stem cell factors mentioned above, which may suggest a reciprocal control of these molecules in astrocytogenesis, where *miR-31* plays a key role [83].

However, based on the PubMed.org database, only 5 studies took into account both types of transcripts, *miR-31* and *MIR31HG*. Tu et al. observed co-upregulation of *miR-31* and *MIR31HG* in oral squamous cell carcinoma, with a linear correlation between both ncRNAs estimated to $R = 0.304$ and $p = 0.047$ in patients' samples [84]. Another study, done by Chang et al. showed that artificial upregulation of *MIR31HG* caused the significant elevation of *MIR31HG* and *miR-31* in two cancer cell lines [85]. Surprisingly, Qin et al., in lung adenocarcinoma, indicated no correlation between *MIR31HG* and *miR-31*, and the down-regulation of *MIR31HG* did not cause decreased levels of *miR-31* [45]. Moreover, some evidence indicates that MIR31HG does not always regulate the level of miR-31. It was pointed out that MIR31HG regulates miR-361 and downstream targets influencing cellular phenotype of osteosarcoma cell lines [37].

It is surprising that for some studies the authors did not analyze the common correlation between *miR-31* and *MIR31HG*, which makes it difficult to assess the actual interaction of these molecules with each other [86].

Not only miR-31, but also other miRNAs interact with MIR31HG

lncRNAs can not only affect protein-coding genes, but also other RNAs. The "sponge effect", as it is commonly known, involves the action of lncRNA on individual miRNAs, which directly results in the reduction of its effect on most mRNAs [44]. Recent studies have shown that *MIR31HG* expression is markedly upregulated in pancreatic ductal adenocarcinoma (PDAC). However, knock-out of this molecule resulted in inhibition of PDAC cell growth, apoptosis, and ultimately reduced invasion. Here, the researchers noted the inverse correlation of *MIR31HG* and *miR-193b* in these cells. When *miR-193b* was overexpressed, *MIR31HG* levels decreased significantly and vice versa. Such results demonstrate the negative regulation of *MIR31HG* by miR-193b. Closer examination using a

luciferase reporter and RIP assays suggested that *miR-193b* bound to *MIR31HG* by blocking the binding sites of this molecule to miRNA. This activity of both molecules speaks to *MIR31HG* acting as a sponge binding *miR-193b* to regulate miRNA targets [87].

Conclusions and future directions

Allis and Jenuwein named RNA "one of the master molecules of epigenetic control" [1]. Not so long ago, ncRNAs were perceived as genetic noise and ignored in all analyses and treated as background or experimental errors [5, 88]. The development of new techniques, such as massive RNA sequencing, bioinformatics and even artificial intelligence (AI), caused an unbelievable growth in the number of discoveries of different types of ncRNA molecules [89, 90]. The public release of data from the The Human Cancer Genome (TCGA) project made it possible to analyze the data in terms of searching for, for example, lncRNA, in 33 different cancers [91, 92]. The TCGA is an immeasurable source of knowledge used as the first source of data for selection of genes and later validated in *in vivo* and *in vitro* models. Unfortunately, not all studies adopt this model of analysis. The lack of validation based on an *in vivo* or *in vitro* model is questionable as an effect of errors accumulation or assumptions of mathematical models. On the other hand, results derived only from *in vivo* or *in vitro* studies can be misleading as the consequences of the cell lines used or the set of patients. It is essential to apply a holistic approach when a study is designed. The lack of comprehensive research causes the knowledge about specific types of ncRNAs still not to be fully defined or validated experimentally. Moreover, many different studies indicated that one lncRNA could behave differently depending on the cancer type [7]. In some cases only one study defines the role of lncRNA in a specific biological process or pathway, which should be verified by independent study. The lack of such an approach is also visible in the case of *MIR31HG*. The second important question concerns the potential use of lncRNA as a biomarker. lncRNAs have all the characteristics of biomarkers, but there are no standardized methods for their measurement and testing [10]. Another issue to consider is which transcript variant should be taken into account. As mentioned earlier, *MIR31HG* has 32 different transcriptional variants, with a length between 287 and 10'980 bp [29]. In some cases, not all variants are equal and they could be expressed in different ways depending on the specific cancer subtype, and have various diagnostic potencies [34]. Most studies regarding not only lncRNAs, but also other types of transcripts, do not explicitly point which transcript variant or variants are being analyzed. Moreover, this information is not included in the TCGA data either. This causes great difficulties in the adaptation of lncRNAs as biomarkers in clinical practice. However,

many studies indicated that lncRNAs may become important tools to predict the development and eventual treatment of cancer in the future [10]. Will they be as useful as classic markers? We assume that the answer to this question will be known within the next decade.

Conflict of interest

Concerning publication of the article titled: Host gene and its guest: short story about relation of long-noncoding MIR31HG transcript and microRNA miR-31, written by Tomasz Kolenda, Anna Paszkowska, Alicja Braska, Joanna Kozłowska-Masłoń, Kacper Guglas, Paulina Poter, Piotr Wojtczak, Renata Bliźniak, Katarzyna Lamperska and Anna Teresiak, the authors declare:

— the contents of this manuscript have not been copyrighted or published previously;
— the contents of the manuscript are not now under consideration for publication elsewhere;
— there is no conflict of interest including financial, personal or other relationships with other people or organizations regarding the publication of this paper;
— this work was supported by Greater Poland Cancer Center — grant No.: 12/2021 (248), 10/11/2021/PGN/WCO/03 and other institutions listed in the acknowledgment.

Financial disclosure

Article titled*: Host gene and its guest: short story about relation of long-noncoding MIR31HG transcript and microRNA miR-31*, written by Tomasz Kolenda, Anna Paszkowska, Alicja Braska, Joanna Kozłowska-Masłoń, Kacper Guglas, Paulina Poter, Piotr Wojtczak, Renata Bliźniak, Katarzyna Lamperska and Anna Teresiak, was supported by the Greater Poland Cancer Center — grant No.: 12/2021 (248), 10/11/2021/PGN/WCO/03 and other institutions listed in the acknowledgment.

Acknowledgment

This work was supported by Greater Poland Cancer Centre – grant No.: 12/2021 (248), 10/11/2021/PGN/WCO/03

While writing this manuscript, Alicja Braska received a “The best in nature 2.0. The integrated program of the Poznań University of Life Sciences” scholarship from University of Life Sciences in Poznań; Joanna Kozłowska-Masłoń received a PhD program scholarship from Adam Mickiewicz University in Poznan; Kacper Guglas received a scholarship from the European Union POWER PhD program; Piotr Wojtczak is a PhD student at Doctoral Studies,

Medical University of Lodz. We would like to thank all the institutions supporting our scientific work.

References

1. Allis CD, Jenuwein T. The molecular hallmarks of epigenetic control. Nat Rev Genet. 2016; 17(8): 487–500, doi: 10.1038/nrg.2016.59, indexed in Pubmed: 27346641.

2. Zhang Y, Yang Li, Chen LL. Life without A tail: new formats of long noncoding RNAs. Int J Biochem Cell Biol. 2014; 54: 338–349, doi: 10.1016/j.biocel.2013.10.009, indexed in Pubmed: 24513732.

3. Furuno M, Pang KC, Ninomiya N, et al. Clusters of internally primed transcripts reveal novel long noncoding RNAs. PLoS Genet. 2006; 2(4): e37, doi: 10.1371/journal.pgen.0020037, indexed in Pubmed: 16683026.

4. Memczak S, Jens M, Elefsinioti A, et al. Circular RNAs are a large class of animal RNAs with regulatory potency. Nature. 2013; 495(7441): 333–338, doi: 10.1038/nature11928, indexed in Pubmed: 23446348.

5. Kozłowska J, Kolenda T, Poter P, et al. Long Intergenic Non-Coding RNAs in HNSCC: From "Junk DNA" to Important Prognostic Factor. Cancers (Basel). 2021; 13(12), doi: 10.3390/cancers13122949, indexed in Pubmed: 34204634.

6. Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. Nat Rev Genet. 2009; 10(3): 155–159, doi: 10.1038/nrg2521, indexed in Pubmed: 19188922.

7. Kolenda T, Guglas K, Ryś M, et al. Biological role of long non-coding RNA in head and neck cancers. Rep Pract Oncol Radiother. 2017; 22(5): 378–388, doi: 10.1016/j.rpor.2017.07.001, indexed in Pubmed: 28794691.

8. Ransohoff JD, Wei Y, Khavari PA. The functions and unique features of long intergenic non-coding RNA. Nat Rev Mol Cell Biol. 2018; 19(3): 143–157, doi: 10.1038/nrm.2017.104, indexed in Pubmed: 29138516.

9. Ransohoff JD, Wei Y, Khavari PA. The functions and unique features of long intergenic non-coding RNA. Nat Rev Mol Cell Biol. 2018; 19(3): 143–157, doi: 10.1038/nrm.2017.104, indexed in Pubmed: 29138516.

10. Guglas K, Bogaczyńska M, Kolenda T, et al. lncRNA in HNSCC: challenges and potential. Contemp Oncol (Pozn). 2017; 21(4): 259–266, doi: 10.5114/wo.2017.72382, indexed in Pubmed: 29416430.

11. Kelley D, Rinn J. Transposable elements reveal a stem cell-specific class of long noncoding RNAs. Genome Biol. 2012; 13(11): R107, doi: 10.1186/gb-2012-13-11-r107, indexed in Pubmed: 23181609.

12. Hoffmann MJ, Dehn J, Droop J, et al. Truncated Isoforms of lncRNA ANRIL Are Overexpressed in Bladder Cancer, But Do Not Contribute to Repression of INK4 Tumor Suppressors. Noncoding RNA. 2015; 1(3): 266–284, doi: 10.3390/ncrna1030266, indexed in Pubmed: 29861427.

13. Smith KN, Miller SC, Varani G, et al. Multimodal Long Noncoding RNA Interaction Networks: Control Panels for Cell Fate Specification. Genetics. 2019; 213(4): 1093–1110, doi: 10.1534/genetics.119.302661, indexed in Pubmed: 31796550.

14. Frankish A, Diekhans M, Ferreira AM, et al. GENCODE reference annotation for the human and mouse genomes. Nucleic Acids Res. 2019; 47(D1): D766–D773, doi: 10.1093/nar/gky955, indexed in Pubmed: 30357393.

15. O'Leary NA, Wright MW, Brister JR, et al. Reference sequence (RefSeq) database at NCBI: current status, taxonomic expansion, and functional annotation. Nucleic Acids Res. 2016; 44(D1): D733–D745, doi: 10.1093/nar/gkv1189, indexed in Pubmed: 26553804.

16. Volders PJ, Anckaert J, Verheggen K, et al. LNCipedia 5: towards a reference set of human long non-coding RNAs. Nucleic Acids Res. 2019; 47(D1): D135–D139, doi: 10.1093/nar/gky1031, indexed in Pubmed: 30371849.

17. Fang S, Zhang L, Guo J, et al. NONCODEV5: a comprehensive annotation database for long non-coding RNAs. Nucleic Acids Res. 2018; 46(D1): D308–D314, doi: 10.1093/nar/gkx1107, indexed in Pubmed: 29140524.

18. Wang W, Min Lu, Qiu X, et al. Biological Function of Long Non-coding RNA (LncRNA) Xist. Front Cell Dev Biol. 2021; 9: 645647, doi: 10.3389/fcell.2021.645647, indexed in Pubmed: 34178980.

19. Kolenda T, Guglas K, Kopczyńska M, et al. Quantification of long non-coding RNAs using qRT-PCR: comparison of different cDNA synthesis methods and RNA stability. Arch Med Sci. 2021; 17(4): 1006–1015, doi: 10.5114/aoms.2019.82639, indexed in Pubmed: 34336028.

20. Dhir A, Dhir S, Proudfoot NJ, et al. Microprocessor mediates transcriptional termination of long noncoding RNA transcripts hosting microRNAs. Nat Struct Mol Biol. 2015; 22(4): 319–327, doi: 10.1038/nsmb.2982, indexed in Pubmed: 25730776.

21. Sun Q, Song YJ, Prasanth KV. One locus with two roles: microRNA-independent functions of microRNA-host-gene locus-encoded long noncoding RNAs. Wiley Interdiscip Rev RNA. 2021; 12(3): e1625, doi: 10.1002/wrna.1625, indexed in Pubmed: 32945142.

22. Kozomara A, Birgaoanu M, Griffiths-Jones S. miRBase: from microRNA sequences to function. Nucleic Acids Res. 2019; 47(D1): D155–D162, doi: 10.1093/nar/gky1141, indexed in Pubmed: 30423142.

23. Ha M, Kim VN. Regulation of microRNA biogenesis. Nat Rev Mol Cell Biol. 2014; 15(8): 509–524, doi: 10.1038/nrm3838, indexed in Pubmed: 25027649.

24. Baskerville S, Bartel DP. Microarray profiling of microRNAs reveals frequent coexpression with neighboring miRNAs and host genes. RNA. 2005; 11(3): 241–247, doi: 10.1261/rna.7240905, indexed in Pubmed: 15701730.

25. Sun Q, Song YJ, Prasanth KV. One locus with two roles: microRNA-independent functions of microRNA-host-gene locus-encoded long noncoding RNAs. Wiley Interdiscip Rev RNA. 2021; 12(3): e1625, doi: 10.1002/wrna.1625, indexed in Pubmed: 32945142.

26. Wong ACH, Rasko JEJ. Splice and Dice: Intronic microRNAs, Splicing and Cancer. Biomedicines. 2021; 9(9), doi: 10.3390/biomedicines9091268, indexed in Pubmed: 34572454.

27. Augoff K, McCue B, Plow EF, et al. miR-31 and its host gene lncRNA LOC554202 are regulated by promoter hypermethylation in triple-negative breast cancer. Mol Cancer. 2012; 11: 5, doi: 10.1186/1476-4598-11-5, indexed in Pubmed: 22289355.

28. HUGO Gene Nomenclature Committee. https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:37187 (2022.02.20).

29. GeneCaRNA: The Human ncRNA Database. https://www.genecards.org/cgi-bin/carddisp.pl?gene=MIR31HG (accessed on 22. (2022.02.20).

30. Nie FQ, Ma S, Xie M, et al. Decreased long noncoding RNA MIR31HG is correlated with poor prognosis and contributes to cell proliferation in gastric cancer. Tumour Biol. 2016; 37(6): 7693–7701, doi: 10.1007/s13277-015-4644-z, indexed in Pubmed: 26692098.

31. Wang Ru, Ma Z, Feng L, et al. LncRNA MIR31HG targets HIF1A and P21 to facilitate head and neck cancer cell proliferation and tumorigenesis by promoting cell-cycle progression. Mol Cancer. 2018; 17(1): 162, doi: 10.1186/s12943-018-0916-8, indexed in Pubmed: 30458787.

32. Xin C, Bi X, Xiao C, et al. MIR31HG regulates the proliferation, migration and invasion of breast cancer by regulating the expression of POLDIP2. J BUON. 2021; 26(2): 459–465, indexed in Pubmed: 34076993.

33. Zheng S, Zhang X, Wang X, et al. MIR31HG promotes cell proliferation and invasion by activating the Wnt/β-catenin signaling pathway in non-small cell lung cancer. Oncol Lett. 2019; 17(1): 221–229, doi: 10.3892/ol.2018.9607, indexed in Pubmed: 30655759.

34. Wu S, Nitschke K, Worst TS, et al. Long noncoding RNA MIR31HG and its splice variants regulate proliferation and migration: prognostic implications for muscle invasive bladder cancer. J Exp Clin Cancer Res. 2020; 39(1): 288, doi: 10.1186/s13046-020-01795-5, indexed in Pubmed: 33334367.

35. Han Y, Yang Q, Huang Y, et al. Mechanical force inhibited hPDLSCs proliferation with the downregulation of MIR31HG via DNA methylation. Oral Dis. 2021; 27(5): 1268–1282, doi: 10.1111/odi.13637, indexed in Pubmed: 32890413.

36. Montes M, Lubas M, Arendrup FS, et al. The long non-coding RNA MIR31HG regulates the senescence associated secretory phenotype. Nat Commun. 2021; 12(1): 2459, doi: 10.1038/s41467-021-22746-4, indexed in Pubmed: 33911076.

37. Sun Y, Jia X, Wang M, et al. Long noncoding RNA MIR31HG abrogates the availability of tumor suppressor microRNA-361 for the growth of osteosarcoma. Cancer Manag Res. 2019; 11: 8055–8064, doi: 10.2147/CMAR.S214569, indexed in Pubmed: 31564967.

38. Feng Bo, Chen Ke, Zhang W, et al. Silencing of lncRNA MIR31HG promotes nasopharyngeal carcinoma cell proliferation and inhibits apoptosis through suppressing the PI3K/AKT signaling pathway. J Clin Lab Anal. 2022; 36(12): e24720, doi: 10.1002/jcla.24720, indexed in Pubmed: 36347827.

39. Gao J, Chen F, Hua M, et al. Knockdown of lncRNA MIR31HG inhibits cell proliferation in human HaCaT keratinocytes. Biol Res. 2018; 51(1): 30, doi: 10.1186/s40659-018-0181-8, indexed in Pubmed: 30180891.

40. Montes M, Nielsen MM, Maglieri G, et al. The lncRNA MIR31HG regulates p16(INK4A) expression to modulate senescence. Nat Commun. 2015; 6: 6967, doi: 10.1038/ncomms7967, indexed in Pubmed: 25908244.

41. Montes M, Lubas M, Arendrup FS, et al. The long non-coding RNA MIR31HG regulates the senescence associated secretory phenotype. Nat Commun. 2021; 12(1): 2459, doi: 10.1038/s41467-021-22746-4, indexed in Pubmed: 33911076.

42. He A, Chen Z, Mei H, et al. Decreased expression of LncRNA MIR31HG in human bladder cancer. Cancer Biomark. 2016; 17(2): 231–236, doi: 10.3233/CBM-160635, indexed in Pubmed: 27434291.

43. Dandan Wu, Jianliang C, Haiyan He, et al. Long noncoding RNA MIR31HG is activated by SP1 and promotes cell migration and invasion by sponging miR-214 in NSCLC. Gene. 2019; 692: 223–230, doi: 10.1016/j.gene.2018.12.077, indexed in Pubmed: 30659947.

44. Ning P, Wu Z, Hu A, et al. Integrated genomic analyses of lung squamous cell carcinoma for identification of a possible competitive endogenous RNA network by means of TCGA datasets. PeerJ. 2018; 6: e4254, doi: 10.7717/peerj.4254, indexed in Pubmed: 29340250.

45. Qin J, Ning H, Zhou Y, et al. LncRNA MIR31HG overexpression serves as poor prognostic biomarker and promotes cells proliferation in lung adenocarcinoma. Biomed Pharmacother. 2018; 99: 363–368, doi: 10.1016/j.biopha.2018.01.037, indexed in Pubmed: 29367106.

46. Liu B, Chen Y, Yang J. LncRNAs are altered in lung squamous cell carcinoma and lung adenocarcinoma. Oncotarget. 2017; 8(15): 24275–24291, doi: 10.18632/oncotarget.13651, indexed in Pubmed: 27903974.

47. Sui J, Yang S, Liu T, et al. Molecular characterization of lung adenocarcinoma: A potential four-long noncoding RNA prognostic signature. J Cell Biochem. 2019; 120(1): 705–714, doi: 10.1002/jcb.27428, indexed in Pubmed: 30125988.

48. Zhang H, Wang Z, Wu J, et al. Long noncoding RNAs predict the survival of patients with colorectal cancer as revealed by constructing an endogenous RNA network using bioinformation analysis. Cancer Med. 2019; 8(3): 863–873, doi: 10.1002/cam4.1813, indexed in Pubmed: 30714675.

49. Eide PW, Eilertsen IA, Sveen A, et al. Long noncoding RNA MIR31HG is a bona fide prognostic marker with colorectal cancer cell-intrinsic properties. Int J Cancer. 2019; 144(11): 2843–2853, doi: 10.1002/ijc.31998, indexed in Pubmed: 30447009.

50. Guo T, Liu D, Peng S, et al. A Positive Feedback Loop of lncRNA MIR31HG-miR-361-3p -YY1 Accelerates Colorectal Cancer Progression Through Modulating Proliferation, Angiogenesis, and Glycolysis. Front Oncol. 2021; 11: 684984, doi: 10.3389/fonc.2021.684984, indexed in Pubmed: 34485123.

51. Qin F, Xu H, Wei G, et al. A Prognostic Model Based on the Immune-Related lncRNAs in Colorectal Cancer. Front Genet. 2021; 12: 658736, doi: 10.3389/fgene.2021.658736, indexed in Pubmed: 33959151.

52. Peng S, Chen L, Yuan Z, et al. Suppression of MIR31HG affects the functional properties of thyroid cancer cells depending on the miR-761/MAPK1 axis. BMC Endocr Disord. 2022; 22(1): 107, doi: 10.1186/s12902-022-00962-3, indexed in Pubmed: 35443670.

53. Chen C, Qin Lu, Xiao MF. Long Noncoding RNA LOC554202 Predicts a Poor Prognosis and Correlates with Immune Infiltration in Thyroid Cancer. Comput Math Methods Med. 2022; 2022: 3585626, doi: 10.1155/2022/3585626, indexed in Pubmed: 35265169.

54. Xu HL, Tian FZ. Clinical significance of lncRNA MIR31HG in melanoma. Eur Rev Med Pharmacol Sci. 2020; 24(8): 4389–4395, doi: 10.26355/eurrev_202004_21020, indexed in Pubmed: 32373976.

55. Chang KW, Hung WW, Chou CH, et al. LncRNA Drives Oncogenicity by Inhibiting the Limb-Bud and Heart Development Gene () during Oral Carcinoma. Int J Mol Sci. 2021; 22(16), doi: 10.3390/ijms22168383, indexed in Pubmed: 34445087.

56. Li Y. MIR31HG exhibits oncogenic property and acts as a sponge for miR-361-3p in cervical carcinoma. Biochem Biophys Res Commun. 2020; 529(4): 890–897, doi: 10.1016/j.bbrc.2020.06.028, indexed in Pubmed: 32819595.

57. Yan S, Tang Z, Chen Ke, et al. Long noncoding RNA MIR31HG inhibits hepatocellular carcinoma proliferation and metastasis by sponging microRNA-575 to modulate ST7L expression. J Exp Clin Cancer Res. 2018; 37(1): 214, doi: 10.1186/s13046-018-0853-9, indexed in Pubmed: 30176933.

58. Yang H, Liu P, Zhang J, et al. Long noncoding RNA MIR31HG exhibits oncogenic property in pancreatic ductal adenocarcinoma and is negatively regulated by miR-193b. Oncogene. 2016; 35(28): 3647–3657, doi: 10.1038/onc.2015.430, indexed in Pubmed: 26549028.

59. Ren ZP, Chu XY, Xue ZQ, et al. Down-regulation of lncRNA MIR31HG correlated with aggressive clinicopathological features and unfavorable prognosis in esophageal squamous cell carcinoma. Eur Rev Med Pharmacol Sci. 2017; 21(17): 3866–3870, indexed in Pubmed: 28975978.

60. Sun K, Zhao X, Wan J, et al. The diagnostic value of long non-coding RNA MIR31HG and its role in esophageal squamous cell carcinoma. Life Sci. 2018; 202: 124–130, doi: 10.1016/j.lfs.2018.03.050, indexed in Pubmed: 29605445.

61. Shih JW, Chiang WF, Wu ATH, et al. Long noncoding RNA LncHIFCAR/MIR31HG is a HIF-1α co-activator driving oral cancer progression. Nat Commun. 2017; 8: 15874, doi: 10.1038/ncomms15874, indexed in Pubmed: 28639619.

62. Li Na, Zhan X. Identification of clinical trait-related lncRNA and mRNA biomarkers with weighted gene co-expression network analysis as useful tool for personalized medicine in ovarian cancer. EPMA J. 2019; 10(3): 273–290, doi: 10.1007/s13167-019-00175-0, indexed in Pubmed: 31462944.

63. Wang XJ, Zeng B, Lin S, et al. An Integrated miRNA-lncRNA Signature Predicts the Survival of Stage II Colon Cancer. Ann Clin Lab Sci. 2019; 49(6): 730–739, indexed in Pubmed: 31882423.

64. Sun T, Guan Q, Wang Y, et al. Identification of differentially expressed genes and signaling pathways in papillary thyroid cancer: a study based on integrated microarray and bioinformatics analysis. Gland Surg. 2021; 10(2): 629–644, doi: 10.21037/gs-20-673, indexed in Pubmed: 33708546.

65. Rajbhandari R, McFarland BC, Patel A, et al. Loss of tumor suppressive microRNA-31 enhances TRADD/NF-κB signaling in glioblastoma. Oncotarget. 2015; 6(19): 17805–17816, doi: 10.18632/oncotarget.4596, indexed in Pubmed: 26164206.

66. Zhou M, Hu L, Zhang Z, et al. Recurrence-Associated Long Non-coding RNA Signature for Determining the Risk of Recurrence in Patients with Colon Cancer. Mol Ther Nucleic Acids. 2018; 12: 518–529, doi: 10.1016/j.omtn.2018.06.007, indexed in Pubmed: 30195788.

67. Feng Lu, Houck JR, Lohavanichbutr P, et al. Transcriptome analysis reveals differentially expressed lncRNAs between oral squamous cell carcinoma and healthy oral mucosa. Oncotarget. 2017; 8(19): 31521–31531, doi: 10.18632/oncotarget.16358, indexed in Pubmed: 28415559.

68. Feng L, Wang Ru, Lian M, et al. Integrated Analysis of Long Noncoding RNA and mRNA Expression Profile in Advanced Laryngeal Squamous Cell Carcinoma. PLoS One. 2016; 11(12): e0169232, doi: 10.1371/journal.pone.0169232, indexed in Pubmed: 28033431.

69. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell. 2005; 120(1): 15–20, doi: 10.1016/j.cell.2004.12.035, indexed in Pubmed: 15652477.

70. Stepicheva NA, Song JL. Function and regulation of microRNA-31 in development and disease. Mol Reprod Dev. 2016; 83(8): 654–674, doi: 10.1002/mrd.22678, indexed in Pubmed: 27405090.

71. Lee EJ, Baek M, Gusev Y, et al. Systematic evaluation of microRNA processing patterns in tissues, cell lines, and tumors. RNA. 2008; 14(1): 35–42, doi: 10.1261/rna.804508, indexed in Pubmed: 18025253.

72. Liu X, Cheng Y, Chen X, et al. MicroRNA-31 regulated by the extracellular regulated kinase is involved in vascular smooth muscle cell growth via large tumor suppressor homolog 2. J Biol Chem. 2011; 286(49): 42371–42380, doi: 10.1074/jbc.M111.261065, indexed in Pubmed: 22020941.

73. Wang J, Yan CH, Li Y, et al. MicroRNA-31 controls phenotypic modulation of human vascular smooth muscle cells by regulating its target gene cellular repressor of E1A-stimulated genes. Exp Cell Res. 2013; 319(8): 1165–1175, doi: 10.1016/j.yexcr.2013.03.010, indexed in Pubmed: 23518389.

74. Li T, Luo W, Liu K, et al. miR-31 promotes proliferation of colon cancer cells by targeting E2F2. Biotechnol Lett. 2015; 37(3): 523–532, doi: 10.1007/s10529-014-1715-y, indexed in Pubmed: 25362258.

75. Karnuth B, Dedy N, Spieker T, et al. Differentially expressed miRNAs in Ewing sarcoma compared to mesenchymal stem cells: low miR-31 expression with effects on proliferation and invasion. PLoS One. 2014; 9(3): e93067, doi: 10.1371/journal.pone.0093067, indexed in Pubmed: 24667836.

76. Zheng W, Liu Z, Zhang W, et al. miR-31 functions as an oncogene in cervical cancer. Arch Gynecol Obstet. 2015; 292(5): 1083–1089, doi: 10.1007/s00404-015-3713-2, indexed in Pubmed: 25894339.

77. He J, Jin S, Zhang W, et al. Long non-coding RNA LOC554202 promotes acquired gefitinib resistance in non-small cell lung cancer through upregulating miR-31 expression. J Cancer. 2019; 10(24): 6003–6013, doi: 10.7150/jca.35097, indexed in Pubmed: 31762810.

78. Cho JH, Dimri M, Dimri GP. MicroRNA-31 is a transcriptional target of histone deacetylase inhibitors and a regulator of cellular senescence. J Biol Chem. 2015; 290(16): 10555–10567, doi: 10.1074/jbc.M114.624361, indexed in Pubmed: 25737447.

79. Hughes DC, Marcotte GR, Baehr LM, et al. Alterations in the muscle force transfer apparatus in aged rats during unloading and reloading: impact of microRNA-31. J Physiol. 2018; 596(14): 2883–2900, doi: 10.1113/JP275833, indexed in Pubmed: 29726007.

80. Capri M, Olivieri F, Lanzarini C, et al. Identification of miR-31-5p, miR-141-3p, miR-200c-3p, and GLT1 as human liver aging markers sensitive to donor-recipient age-mismatch in transplants. Aging Cell. 2017; 16(2): 262–272, doi: 10.1111/acel.12549, indexed in Pubmed: 27995756.

81. Kuosmanen SM, Kansanen E, Sihvola V, et al. MicroRNA Profiling Reveals Distinct Profiles for Tissue-Derived and Cultured Endothelial Cells. Sci Rep. 2017; 7(1): 10943, doi: 10.1038/s41598-017-11487-4, indexed in Pubmed: 28887500.

82. Li P, Gao Y, Li X, et al. mRNA and miRNA expression profile reveals the role of miR-31 overexpression in neural stem cell. Sci Rep. 2020; 10(1): 17537, doi: 10.1038/s41598-020-74541-8, indexed in Pubmed: 33067542.

83. Meares GP, Rajbhandari R, Gerigk M, et al. MicroRNA-31 is required for astrocyte specification. Glia. 2018; 66(5): 987–998, doi: 10.1002/glia.23296, indexed in Pubmed: 29380422.

84. Tu HF, Liu CJ, Hung WW, et al. Co-upregulation of and its host gene lncRNA in oral squamous cell carcinoma. J Dent Sci. 2022; 17(2): 696–706, doi: 10.1016/j.jds.2021.11.006, indexed in Pubmed: 35756773.

85. Chang KW, Hung WW, Chou CH, et al. LncRNA Drives Oncogenicity by Inhibiting the Limb-Bud and Heart Development Gene () during Oral Carcinoma. Int J Mol Sci. 2021; 22(16), doi: 10.3390/ijms22168383, indexed in Pubmed: 34445087.

86. Cai P, Li H, Huo W, et al. Aberrant expression of LncRNA-MIR31HG regulates cell migration and proliferation by affecting miR-31 and miR-31* in Hirschsprung's disease. J Cell Biochem. 2018; 119(10): 8195–8203, doi: 10.1002/jcb.26830, indexed in Pubmed: 29626357.

87. Yang H, Liu P, Zhang J, et al. Long noncoding RNA MIR31HG exhibits oncogenic property in pancreatic ductal adenocarcinoma and is negatively regulated by miR-193b. Oncogene. 2016; 35(28): 3647–3657, doi: 10.1038/onc.2015.430, indexed in Pubmed: 26549028.

88. Stasiak M, Kolenda T, Kozłowska-Masłoń J, et al. The World of Pseudogenes: New Diagnostic and Therapeutic Targets in Cancers or Still Mystery Molecules? Life (Basel). 2021; 11(12), doi: 10.3390/life11121354, indexed in Pubmed: 34947885.

89. Story MD, Durante M, Norbury JW, et al. Galactic cosmic ray simulation at the NASA Space Radiation Laboratory. Life Sci Space Res (Amst). 2016; 8(11): 38–51, doi: 10.1016/j.lssr.2016.02.001, indexed in Pubmed: 26948012.

90. Schofield PN, Kulka U, Tapio S, et al. Big data in radiation biology and epidemiology; an overview of the historical and contemporary landscape of data and biomaterial archives. Int J Radiat Biol. 2019; 95(7): 861–878, doi: 10.1080/09553002.2019.1589026, indexed in Pubmed: 30888231.

91. Tomczak K, Czerwińska P, Wiznerowicz M. The Cancer Genome Atlas (TCGA): an immeasurable source of knowledge. Contemp Oncol (Pozn). 2015; 19(1A): A68–A77, doi: 10.5114/wo.2014.47136, indexed in Pubmed: 25691825.

92. Kozłowska-Masłoń J, Guglas K, Paszkowska A, et al. Radio-lncRNAs: Biological Function and Potential Use as Biomarkers for Personalized Oncology. J Pers Med. 2022; 12(10), doi: 10.3390/jpm12101605, indexed in Pubmed: 36294743.

Figure 1. Two main branches of epigenetics elements involved in cell function can be distinguished and they are based on DNA and RNA level. On the DNA level, three main changes include: **A.** DNA methylation: which involves changes in methylation by adding methyl groups to the DNA molecule and when appeared in the promoter region; **B.** histone modification which is a chemical modification of amino acids that build the histone proteins causing changes in specific genes' regions; and **C.** Chromatin remodeling: which causes changes in chromatin structure and generates accessible and no-accesible parts' of the genome. On the RNA level it is the production of different types of non-coding RNA molecules which are involved in: **D.** Regulation of mRNA and ncRNA levels by sponging mechanism and influencing transcription process; and **E.** Modification of RNA molecules by

capping, polyadenylation, alternative splicing, and editing. All of these processes cause modifications in gene transcription

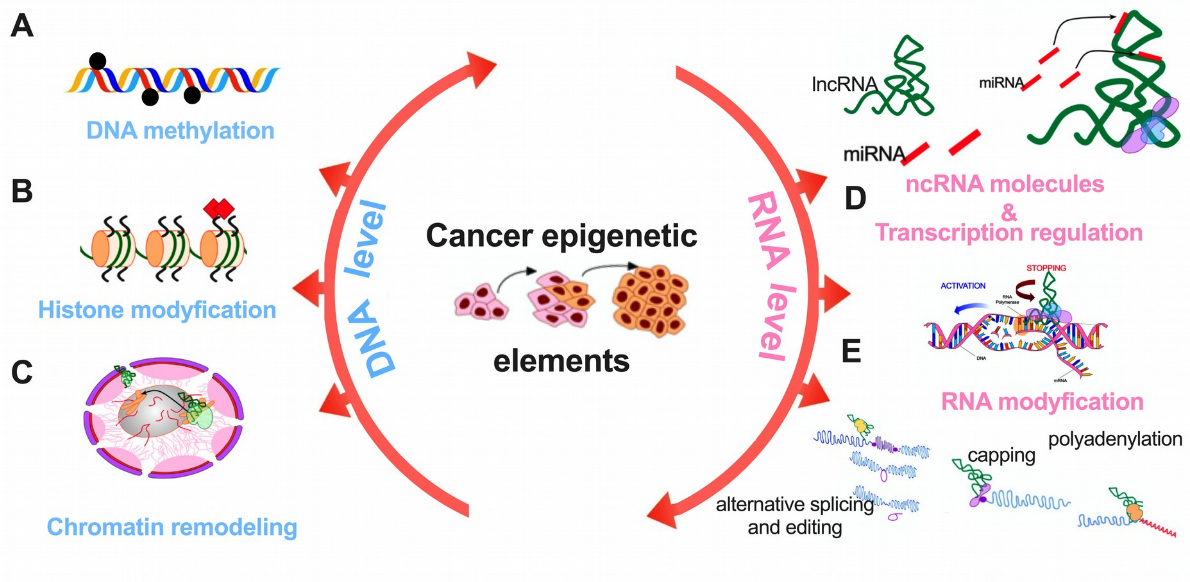


Figure 2. MIR31HG functions as a modulator of important biological and cellular processes including cell proliferation, apoptosis, cell cycle regulation, EMT process, metastasis, angiogenesis, hypoxia, senescence, and inflammation.

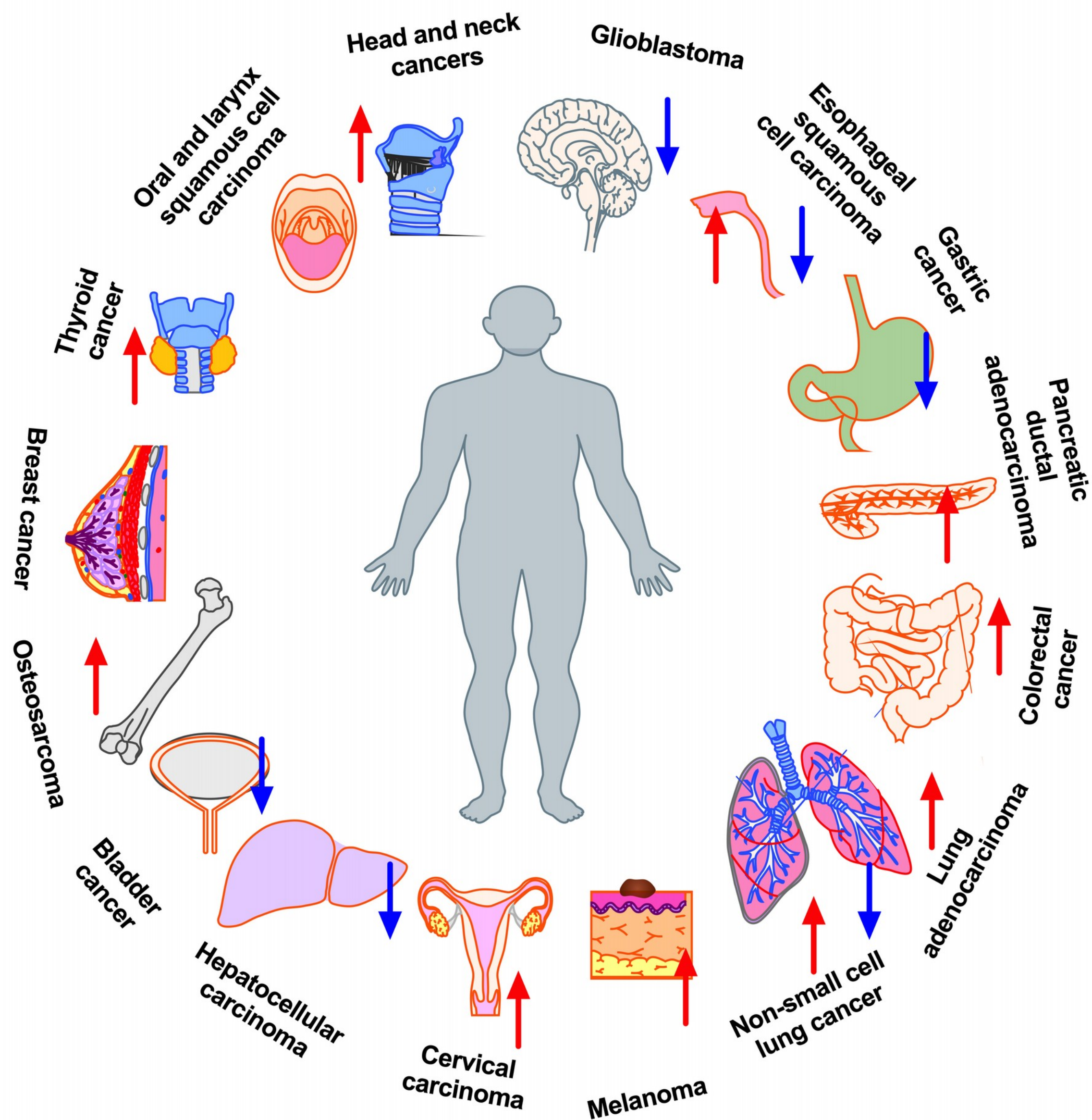
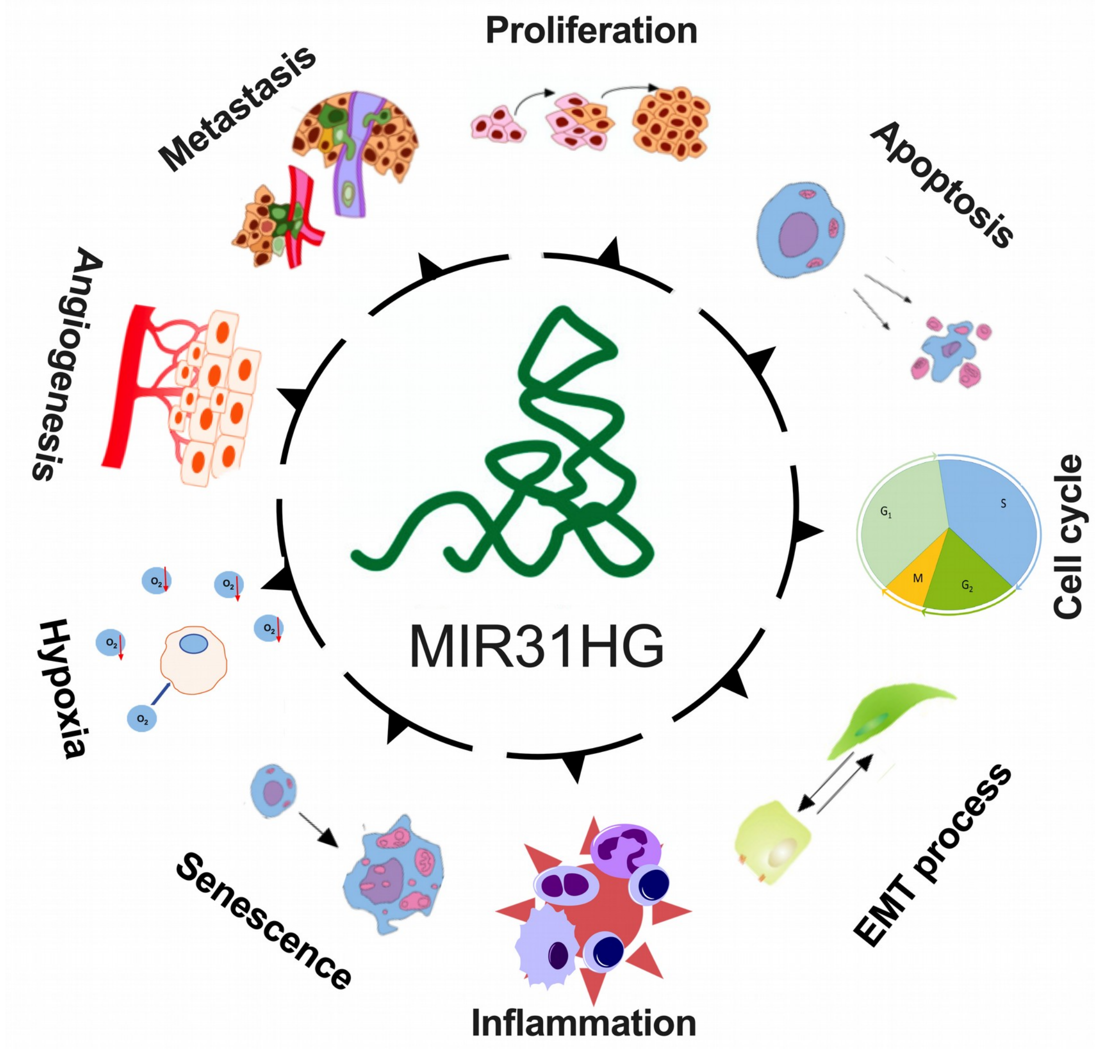


Figure 3. Dysregulation and function of MIR31HG as a potential biomarker in different types of cancers. Red arrows indicate an increase, and blue, a decrease in the level of MIR31HG expression in a tumor of a given location


Proliferation
Apoptosis
Cell cycle
EMT process
Inflammation
Senescence
Hypoxia
Angiogenesis
Metastasis
MIR31HG