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Functions and mechanisms of microRNA-31 in human cancers

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ABSTRACT

MicroRNAs can exhibit opposite functions in different tumors. MiR-31 is a representative example as it can not only enhance tumor development and progression in pancreatic cancer, colorectal cancer and so on, but also inhibit tumorigenesis and induce apoptosis in ovarian cancer, prostate cancer and etc. The mechanism underlying its' pleiotropy remains unknown. Several recent studies that focused on the global gene expression changes caused by aberrant miR-31 provided information on the upstream and downstream events associated with deregulated miR-31. MiR-31 might interact with a number of signaling pathways including RAS/MARK, PI3K/AKT and RB/E2F to play its opposite functions. This review summarizes the target genes and pathways associated with miR-31 and examines the mechanisms underlying the function of miR-31. The resulting hypothesis is possible that the tissue-specific features of adenocarcinoma and squamous cell cancer and the positive feedback loop consists of miR-31 and its upstream and downstream may account for the diversity of miR-31 functions.

1. Introduction

MicroRNAs (miRNAs) are noncoding RNAs of 21–25 nucleotides that in combination with Argonaute proteins play a critical role in regulating the expression of mRNAs by forming the RNA-induced silencing complex. MiRNAs bind to the 3′-untranslated region (3′-UTR) of mRNAs, activating the RNA-induced silencing complex to inhibit the translation or degrade the mRNA directly. MiRNAs participate in many processes, including cell proliferation, migration, and apoptosis. MiRNAs implicated in tumorigenesis and tumor progression are called oncomiRs. Evidence indicates that miR-21, which targets *PTEN*, *TPM1*, and *PDCD4* in breast tumors [1], is oncogenic. However, miR-15a and miR-16, which target *BCL-2* in chronic lymphocytic leukemia [2], and miR-532, which targets *KRAS* in lung adenocarcinoma (ADC) cells [3] are tumor suppressive.

Research on miR-31 shows that it displays altered levels of expression in different tumors. The *miR-31* gene is located on chromosome band 9p21.3, ~500 kb from the locus of the well-known tumor suppressors cyclin dependent kinase inhibitor *(CDKN)2A* and *CDKN2B*, which encode the cell cycle inhibitor proteins p15 and p16 [4]. Because of their proximity, it is reasonable to suppose that miR-31 would be lost together with CDKN2A in various types of cancer. Besides the gene loci loss, epigenetic modifications like the hyper-methylation caused by EZH2 are also responsible for the low expression of miR-31. The expression of miR-31 is reduced in breast, ovarian, and prostate cancers and in hepatocellular and gastric carcinoma. By contrast, some oncogenic molecular like KRAS can stimulate the promoter of miR-31 and elevate its level. MiR-31 is overexpressed in lung, colorectal, non-small-

Abbreviations: 3′-UTRs3′, -untranslated regions; ADC, Adenocarcinoma; BC, Breast cancer; BER, base excision repair; CDK4, cyclin-dependent kinase 4; CRC, Colorectal cancer; CRT, chemo-radiation therapy; C-TAD, COOH terminal transactivation domain; DHR1, dihydrorhodamine 1; DSB, double strain break; EBV, Epstein-Barr virus; EMT, epithelial-mesenchymal transition; EndMT, endothelial–mesenchymal transition; ER, estrogen receptor; ESCC, Esophageal squamous cell carcinoma; FIH, factor-inhibiting hypoxia-inducible factor; GC, Gastric cancer; GEF, guanine nucleotide exchange factor; HCC, Hepatocellular carcinoma; HER-2, human epithelial growth factor receptor-2; HIF, hypoxia-inducible factor; HNSCC, Head and neck squamous cell carcinoma; ICC, Intrahepatic cholangiocarcinoma; ISCs, Intestinal stem cells; ITGA5, integrin α5; MASC, mammary stem cell; MIRNA, microRNA; MLC, myosin light chain; MMR, mismatch repair; MSI, microsatellite instability; NER, nucleotide excision repair; NPC, Nasopharygeal carcinoma; NSCLC, Non-small-cell lung carcinomas; NT, nucleotide; OAC, Oesophageal adenocarcinoma; OSCC, Oral squamous cell carcinoma; OPMD, oral potentially malignant disorder; PCA, Prostate cancer; PKCε, protein kinase C epsilon; PR, progesterone receptor; RB, retinoblastoma protein; RISC, RNA-induced silencing complex; S1P, Sphingosine-1-phosphate; SCC, squamous cell carcinoma; STK40, serine threonine kinase 40; TFs, transcription factors; TIAM1, T lymphoma invasion and metastasis 1; TNBC, Triple negative breast cancer; VEGF, vascular endothelial growth factor; ZD, Zn deficiency

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Table 1
Down-regulated miR-31 in human cancer showing tumor repressive function.

Cancer	MiR-31	Gene	Pathway	Function	Refs
Ovarian cancer	DOWN	*E2F2* *CEBPA* *STK40*	Cell cycle (E2F) P53	Anti-proliferation	[6]
		MET	PI3K/AKT	Chemo-sensitivity	[7]
HCC	DOWN	*HDAC2* *CDK2*	Cell cycle (E2F) P53	Anti-proliferation	[9]
PCA	DOWN	*E2F1* *E2F2* *EXO1* *FOXM1* *MCM2*	Cell cycle (E2F)	Anti-proliferation	[11]
		AR	AR		
NPC	DOWN	*MCM2* *FIH*	Cell cycle P53	Anti-proliferation Anti-migration	[12]
OAC	DOWN	*PARP1* *SMUG1* *MLH1* *MMS19*	DNA repairing pathways	Radio-sensitivity	[14]
GC	DOWN	*RhoA* *ITGA5* *Smad4* *SGPP2*	Rho/ROCK PI3K/AKT TGF* STAT3*	Anti-migration Anti-migration Anti-proliferation Anti-migration Apoptosis	[15,18,20],21,22]
		E2F2	Cell cycle (E2F)*	Anti-proliferation	
Glioma	DOWN	*DOCK1*	NF-κB	Anti-migration	[23]
BC	DOWN	*PRKCE*	NF-κB	Apoptosis Chemo/radio-sensitivity	[25]
	UP	*Smad3* *Smad4*	TGF-β△	Proliferation	[26]
		Axin1 *Dkk1* *Gsk3β*	WNT△		

In some circumstances, although miR-31 can directly regulate the key genes of specific pathways, whether miR-31 does participate in them or not have not been proved by experiments yet. We mark these pathways with"*" to distinguish like the TGF pathway in GC.
And the pathways where miR-31 shows contradictory functions in the same organ are marked with "△".

cell lung, head and neck squamous cell, and esophageal squamous cell cancers, indicating its oncogenic ability. This paradox suggests the temporal-spatial specificity of miR-31, although the underlying mechanism is still unclear.

To explore the elements responsible for the diverse expression of miR-31, our previous study conducted an integrative analysis of miR-31 to predict targets and pathways using a computational algorithm and obtained a list of hub genes and 163 pathways. Of these, the following eight were selected as significant pathways [5]: cell cycle; axon guidance; RNA polymerase; pathways in cancer; base excision repair; tight junction; Keratan sulfate biosynthesis; and T cell receptor signaling pathway. This systematic analysis improves our knowledge of miR-31 and provides a basis for detailed study of miR-31. In the present review, miR-31 target genes and associated signaling were identified and compared to elucidate the mechanisms underlying the different functions of miR-31 in different malignancies.

2. Tumor suppressor

When miR-31 is downregulated in human cancer (Table 1), it usually plays a tumor suppressive role by targeting specific genes in different pathways (Fig. 1). Among them, RB/E2F and P53 pathways appear in almost all of the following cases. The ability of miR-31 to induce apoptosis and retrieve chemo-/radio-sensitivity also makes it a possible antineoplastic drug in special circumstances.

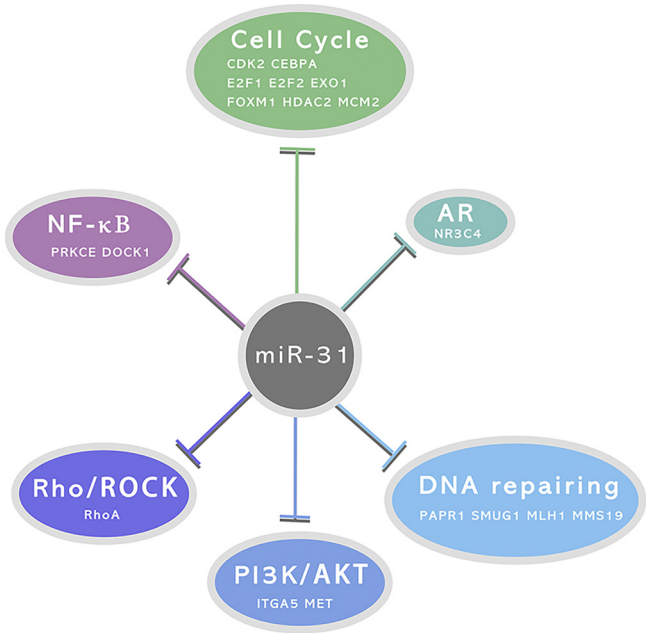

Fig. 1. Integrative analysis of miR-31 target genes and pathways (functions as a tumor suppressor).
This illustration shows 6 miR-31 related signaling pathways where miR-31 suppresses tumorigenesis and development via targeting genes involved in those pathways.

2.1. Ovarian cancer

MiR-31 may share features with tumor suppressor p16, as it is located near *CDKN2A* on chromosome 9p21. MiR-31 loss occurs in serous ovarian cancer [6]. Serine threonine kinase 40 (*STK40*), *CEBPA*, and *E2F2* are suppressed by miR-31 overexpression in ovarian cancer cells. STK40 is a repressor of p53-mediated transcription. CEBPA is linked to alterations in E2F complexes and the E2F pathway in prostate cancer [7]. E2F2 is a transcription factor involved in the E2F pathway. Considering that miR-31 overexpression inhibits the proliferation of serous ovarian cancer cells with a mutated p53 pathway, whereas it has no effect on p53 function in cancer cells, the relationship between miR-31 and the E2F and p53 pathways should be studied further.

The E2F pathway is involved in the G1/S transition of the cell cycle. The pocket protein retinoblastoma protein (RB) can bind with E2F to mask the activation of transcription. MiR-31 may arrest cells in G1 phase by targeting *E2F2* and *CEBPA*. The p53 pathway is a canonical route to repress cancer by inactivating E2F with pRB or inducing cell apoptosis. Therefore, in a cell line with an inactive p53 pathway containing mutated *TP53* or impaired *CDKN2A*, when E2F2 is overexpressed and the E2F pathway is constantly activated, there are no rescue factors to antagonize proliferation. Cell lines without a functional p53 pathway are vulnerable to the expression of miR-31, as miR-31 can downregulate E2F2 to block the cell cycle. By contrast, cancer cells with a functional p53 pathway or those that are not driven by *E2F2* are resistant to miR-31. The mechanism underlying p53 function may partly explain the different functions of miR-31.

Additionally, miR-31 can antagonize the chemical resistance in ovarian cancer cells through the translational inhibition of MET, a hepatocyte growth factor receptor tyrosine kinase [7]. Ovarian cancer cells with taxanes resistance express low miR-31 level, while overexpressing miR-31 can reduce protein levels of MET and re-sensitize those cells. As there is mounting evidence profiling that X-chromosome-linked inhibitor of apoptosis (XIAP) contributes to chemo-resistance in