

SNHG15: a promising cancer-related long noncoding RNA

This article was published in the following Dove Press journal:
Cancer Management and Research

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Abstract: Cancer is expected to rank as the leading cause of death worldwide due to increasing morbidity and mortality. Long noncoding RNAs (lncRNAs) have been found to play pivotal roles in multiple biological processes, such as transcriptional interference, posttranscriptional regulation and epigenetic modification. Small nucleolar RNA host gene 15 (SNHG15), a snoRNA host gene which produces a short half-lived lncRNA, was reported to be upregulated in tumor cells and participate in the occurrence and development of multiple cancers. And more than half of the SNHG15 research in cancers has been published within the last 2 years. In this review, we summarized the current evidence concerning the biological functions and molecular mechanisms of SNHG15 in various cancers, including gastric, hepatocellular, pancreatic, colorectal, breast, and thyroid cancer, osteosarcoma, glioma, lung cancer, renal cell carcinoma, and epithelial ovarian cancer. SNHG15 plays critical roles in regulation of cell proliferation, migration and invasion of tumors via different potential mechanisms. Moreover, the abnormal expression of SNHG15 was associated with clinical features of patients with cancers. Consequently, SNHG15 could be considered as a promising biomarker for cancer diagnosis, prognosis or treatment.

Keywords: SNHG15, long noncoding RNA, cancer, biomarker

Introduction

As the incidence and mortality increase, cancer has become a major public health problem and ranked as the leading cause of death all over the world. It is estimated that 18,078,957 new cancer cases and 9,555,027 cancer deaths will happen in the world in 2018¹ and 1,735,350 new cancer cases and 609,640 cancer deaths will occur in the United States in 2018.² Although great advancement has been achieved in the treatment of cancer, such as surgery, chemotherapy, radiotherapy, immunotherapy and targeted therapy, advanced-stage cancers still have a poor 5-year survival rate and high death rate.³ Therefore, there is a pressing need to identify potential diagnostic and prognostic biomarkers as well as investigate the molecular mechanisms in cancer, which may play an essential role in the clinical treatment of cancer patients.

According to eukaryote whole-genome sequencing, only 2% genes are related to protein coding, while the rest are noncoding RNAs (ncRNAs).⁴ Among these ncRNAs, lncRNAs are initially considered as transcriptional noise with >200 nucleotides and lack protein-coding potential.⁵⁻⁷ Recently, increasing evidence reveals that lncRNAs function as promising oncogenes, or tumor-suppressor genes,^{8,9} taking part in various biological processes, such as cell proliferation, migration, invasion, cell cycle arrest, apoptosis, metastasis, etc.¹⁰⁻¹³ For instance, MALAT1 in NSCLC¹⁴ and ESCC,¹⁵ ZFAS1 in breast cancer¹⁶ and etc. Till now, only a few of lncRNAs have

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been well studied, and the majority of the lncRNAs still remain unknown, which needs to be further investigated.

Small nucleolar RNA host gene 15 (SNHG15), located on chromosome 7p13, which was first characterized by Tani et al in the study of cellular stress responses as a short half-life lncRNA,^{17–19} is a novel lncRNA. Recently, it has been reported that SNHG15 is associated with various kinds of cancers. Chen et al first found that SNHG15 was overexpressed in gastric cancer (GC) in 2016²⁰ and confirmed to be associated with cancer progression. Soon afterward, overexpression of SNHG15 was proved to be linked with poor survival in many human malignancies, including breast cancer, colorectal cancer (CRC), GC, glioma, hepatocellular cancer, lung cancer, osteosarcoma (OS), ovarian cancer, pancreatic cancer (PC), renal cell carcinoma (RCC) and thyroid cancer.^{20–36} Overview of SNHG15 in human cancers may provide a new perspective to study the mechanisms of cancer development. In this review, we mainly summarize the recent progression of SNHG15 correlated with cancer clinicopathological features and regulation mechanisms in the development and progression of multiple cancers (Tables 1 and 2).

SNHG15 in human cancers

Breast cancer

Breast cancer, one of the most frequent cancers in females, is the second mortality-related malignant cancers in women after lung cancer.³⁷ Progressive therapeutics have revolutionized the treatment of breast cancer. However, distant metastasis still remains the major problem of deterioration in breast cancer patients.³⁸

Kong et al²¹ found that SNHG15 was significantly increased in 58 breast cancer tissues and 5 cell lines, and upregulated SNHG15 expression was positively associated with larger tumor size, lymph node metastasis and advanced TMN stage. Besides, Kaplan–Meier analysis revealed that breast cancer patients with elevated SNHG15 expression had a worse survival. Then, knockdown of SNHG15 had a negative effect on cell proliferation, migration and invasion but a positive effect on cell cycle arrest and apoptosis of breast cancer cells. Further studies showed that cells with SNHG15-depleted had lower expression of MMP2, MMP9, SNAI1, vimentin but enhanced expression of E-cadherin, which indicated the inhibition of the cell migration and invasion, as well as epithelial to the mesenchymal transition (EMT) process. Furthermore, the mechanism investigation revealed that SNHG15 acts as a competing endogenous RNA

(ceRNA) to sponge miR-211-3p, leading to the proliferation, migration and invasion of breast cancer cells.

In conclusion, SNHG15 may serve as a prognostic biomarker for breast cancer patients, and SNHG15 sponging miR-211-3p might play an essential role in the pathogenesis of breast cancer.

Colorectal cancer

CRC is the third most prevalent form of malignancies among males and females in the United States and ranked fourth in cancer patient death.³⁹ Though incidence and mortality rates have been declining mainly due to early diagnoses by screening tests and improvements of standard treatment,⁴⁰ the occurrence of relapse and metastasis still influence the prognosis of CRC patients.

Jiang et al²² reported that SNHG15 was noted to be upregulated in colon adenocarcinoma (COAD) samples according to TCGA datasets, and upregulated SNHG15 was also observed in higher grade colon cancer cells compared with lower grade cells. Analysis of clinical data from TCGA also demonstrated that upregulated SNHG15 expression was related to a worse overall survival in patients with COAD. In addition, overexpression of SNHG15 facilitated cell migration and accelerated tumor growth in vivo. Moreover, SNHG15 maintains the stability of Slug in colon cancer cells by inhibiting its ubiquitination and degradation via interaction with the zinc finger domain of Slug.

Huang et al²³ similarly revealed that SNHG15 was overexpressed in 91 CRC tissues compared with those in paired normal tissues. Enhanced expression of SNHG15 was significantly linked with liver metastasis, lymph node metastasis, advanced TMN stage and poor overall survival.

Taken together, upregulated SNHG15 in CRC was an independent predictor of poor survival, and oncogenic lncRNA SNHG15 may be a therapeutic target in colon cancer patients.

Gastric cancer

According to the latest statistics, GC is the fourth leading cause of human malignant disease, and the second most common cancer death worldwide,¹ with definitely high incidence in Eastern Asia.^{41,42} Although advanced diagnosed methods and treatment have been established, most patients are still diagnosed at an advanced stage, which results in dismal prognosis.⁴³ Thus, it is of great significance to identify key biomarkers and illustrate the molecular mechanisms of GC progression.

Table 1 Functional characterization of SNHG15 in various cancers

Cancer types	Expression	Functional roles	Related genes	Role	References
Breast cancer	Upregulated	Proliferation, migration, invasion, cell cycle arrest, apoptosis, EMT	MIR-211-3p, E-cadherin, vimentin, MMP2, MMP9, SNAI1	Oncogenic	21
Colorectal cancer	Upregulated	Migration, EMT, tumor growth	Slug, E-cadherin	Oncogenic	22,23
Gastric cancer	Upregulated	Proliferation, migration, invasion, apoptosis, tumorigenesis	MMP2, MMP9	Oncogenic	20
Glioma	Upregulated	Proliferation, migration, angiogenesis	MIR-153, VEGFA, Cdc42	Oncogenic	24
Lung cancer	Upregulated	Proliferation, migration, invasion, cell cycle arrest, apoptosis, EMT	MIR-486, miRNA-211-3p, CDK14, BAX, Bcl-2, cleaved caspase-3, PARP, E-cadherin, N-cadherin, Vimentin, MMP-2, MMP-9	Oncogenic	26–28
Osteosarcoma	Upregulated	Proliferation, migration, invasion, autophagy	MIR-141, Atp5, LC3-II, p62	Oncogenic	29
Epithelial ovarian cancer	Upregulated	Proliferation, migration, invasion, drug resistance	—	Oncogenic	30
Pancreatic cancer	Upregulated	Proliferation, apoptosis, cell cycle arrest, tumorigenesis	EZH2, H3K27me3, P15, KLF2, CDK2, CDK4, cleaved caspase-3, cleaved caspase-9	Oncogenic	31,32
Renal cell cancer	Upregulated	Proliferation, migration, invasion, cell cycle arrest, apoptosis, EMT	TNF- α , Snail1, Slug, ZEB1, E-cadherin, N-cadherin, Vimentin	Oncogenic	33
Thyroid cancer	Upregulated	Proliferation, migration, apoptosis, EMT	MIR-200a-3p, YAPI, MST1, LATS1, E-cadherin, N-cadherin, Vimentin, β -catenin	Oncogenic	34
	Downregulated	Proliferation, migration, invasion	MIR-510-5p	Nononcogenic	35,36

Abbreviations: EMT, Epithelial to mesenchymal transition; MMP, matrix metalloproteinase; SNAI1, snail family transcriptional repressor 1; VEGFA, vascular endothelial growth factor A; Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; PARP, poly(ADP-ribose) polymerase; EZH2, enhancer of zeste homolog 2.

Table 2 Clinical significance of SNHG15 in various cancers

Cancer types	Clinicopathologic features	References
Breast cancer	Tumor size, lymph node metastasis, advanced TMN stage, poor survival	21
Colorectal cancer	Liver metastasis, lymph node metastasis, advanced TMN stage, poor overall survival	22,23
Gastric cancer	Invasion depth, advanced TNM stage, lymph node metastasis, poor overall survival, poor disease-free survival	20
Hepatocellular cancer	Histological grade, vein invasion, TNM stage, poor survival	25
Lung cancer	Tumor size, lymph node metastasis, advanced TMN stage, poor survival	26–28
Epithelial ovarian cancer	Cancer type, ascites, FIGO stage, poor overall survival, poor progression-free survival	30
Pancreatic cancer	Tumor size, lymph node metastasis, advanced TMN stage, tumor differentiation, poor overall survival	31,32
Renal cell cancer	Histological differentiation, advanced T stage, poor survival	33
Thyroid cancer	Tumor size, lymph node metastasis, advanced TMN stage, poor survival	34

Abbreviations: TMN, tumor node metastasis; FIGO, Federation of Gynecology and Obstetrics.

Chen et al²⁰ proved that SNHG15 was markedly overexpressed in 106 GC tissues and 5 cell lines compared with that in corresponding normal tissues and a normal gastric epithelial cell line, respectively. Upregulated SNHG15 was closely linked with invasion depth, advanced TNM stage and lymph node metastasis. Kaplan–Meier analysis showed that enhanced SNHG15 contributed to poor overall survival and poor disease-free survival of GC patients. Biologically, knocking down SNHG15 inhibited cell proliferation, migration and invasion but induced apoptosis in GC cell lines. Moreover, enhanced SNHG15 was verified to induce tumorigenesis of GC cells in vivo. More importantly, SNHG15 promoted cell proliferation and invasion in GC cell lines partly by increasing MMP2 and MMP9 protein expression.

These data suggested that SNHG15 displayed potential to work as a poor prognostic biomarker in GC patients.

Glioma

Glioma is believed to be the most common form of adult primary malignant brain tumor.⁴⁴ Despite treated with surgery, chemotherapy and radiotherapy, glioma patients still have a high recurrent rate and the prognosis remains poor.⁴⁵ Thus, it is urgent to elucidate the molecular mechanisms and seek effective biomarkers for the treatment of this disease.

Ma et al²⁴ illustrated that SNHG15 expression levels were notably upregulated in glioma vascular endothelial cells compared with primary astrocyte cells. And silencing SNHG15 dramatically suppressed cell proliferation, migration and angiogenesis of glioma vascular endothelial cells. Moreover, miR-153 was low expressed in glioma vascular endothelial cells, while VEGFA and Cdc42 were

upregulated. Additionally, patients with glioma of overexpressed SNHG15 tended to have poorer overall survival, while patients with overexpressed miR-153 tended to have better overall survival. Furthermore, SNHG15 was confirmed to bind with miR-153 and negatively regulating its function, and miR-153 was found to be directly targeted the 3'-UTR of VEGFA and Cdc42 by bioinformatic databases and dual-luciferase reporter assay. Thus, knocking down SNHG15 downregulated VEGFA and Cdc42 expression via targeting miR-153, suppressing glioma vascular endothelial cell proliferation, migration and angiogenesis.

These findings indicated that SNHG15 and miR-153 could be novel potential therapeutic targets for antiangiogenesis therapy of glioma.

Hepatocellular cancer

Hepatocellular carcinoma (HCC) is considered to be the most prevalent primary malignancies of the liver and is the third leading cause of cancer-related deaths worldwide.^{46,47} Numerous patients are diagnosed at an advanced stage, which limits therapeutic options and affects prognosis.⁴⁸ Therefore, identifying effective biomarkers for early diagnosis in HCC patients is urgently needed.

Zhang et al²⁵ stated that the expression level of SNHG15 was significantly higher in 152 HCC tissues than in adjacent normal tissues. Overexpressed SNHG15 was correlated with histological grade, vein invasion and TNM stage. Kaplan–Meier analysis revealed that enhanced SNHG15 was associated with poor overall survival of patients.

Collectively, the above study showed that SNHG15 may act as an efficient biomarker for HCC patients' prognosis and a therapeutic target for HCC.

Lung cancer

Lung cancer is the most aggressive malignant cancer among both men and women, leading to 11.6% new cases and 18.4% cancer deaths in 2018 worldwide.¹ Non-small cell lung cancer (NSCLC) accounts for about 85% of lung cancers; though patients are treated with surgery, chemotherapy and radiotherapy, the overall survival rate of patients with late stage is still dissatisfying.⁴⁹ Therefore, it is of great importance to identify novel biomarkers for lung cancer treatment.

Jin et al²⁶ elucidated that SNHG15 was markedly increased in NSCLC tissue samples ($p < 0.01$) and 4 NSCLC cell lines compared with those in corresponding normal tissue samples and a normal human bronchial epithelial cell line. Upregulated SNHG15 was associated with lymph node metastasis, advanced TMN stage and poor overall survival. Further experiments revealed that SNHG15 silencing inhibited cell proliferation but promoted apoptosis and induced cell cycle arrest at G0/G1 phase. Meanwhile, SNHG15 silencing also inhibited the tumor growth of NSCLC cells in vivo. Mechanically, miR-486 was revealed to target SNHG15 3'-UTR with molecular binding and 3'-UTR of CDK14 with complementary binding sites via bioinformatics prediction tools and luciferase reporter assay.

Dong et al²⁷ also uncovered that the expression level of SNHG15 was significantly higher in 49 NSCLC tissues than in paired para-carcinoma tissue. Besides, upregulated SNHG15 was dramatically related to tumor size, lymph node metastasis, advanced TMN stage, poor disease-free survival and poor overall survival. Silencing SNHG15 inhibited proliferation, migration, invasion and EMT process but induced apoptosis.

Cui et al²⁸ similarly revealed that SNHG15 was upregulated in 55 lung cancer tissues and 3 lung cancer cell lines, and patients with a high level of SNHG15 had worse clinical outcomes. Knocking down SNHG15 could depress the proliferation and migration and invasion of lung cancer cells and induced cell cycle arrest in G0/G1 phase. Furthermore, mechanical experiment indicated that SNHG15 promoted the occurrence of lung cancer through regulating miRNA-211-3p.

In conclusion, SNHG15 may serve as a novel pathogenesis and potential therapeutic target for lung cancer patients.

Osteosarcoma

OS is one of the most prevalent form of primary bone cancers worldwide that mostly affects children,

adolescents and young adults.² The treatment of OS has improved greatly during the last 40 years, including neoadjuvant chemotherapy followed by surgical treatment. However, large amounts of patients are insensitive to chemotherapy, and the recurrent rate is still very high.⁵⁰ Therefore, identifying novel therapeutic biomarkers is urgently needed.

Liu et al²⁹ corroborated that SNHG15 expression level was dramatically increased in 35 OS tissues and 5 OS cell lines compared with paired normal tissues and osteoblastic cell line. Meanwhile, expression of miR-141 was remarkably decreased in 35 OS tissues and SNHG15 was negatively linked with the expression of miR-141 in OS tissues. Biologically, SNHG15 knockdown notably attenuated cell proliferation, migration, invasion and autophagy. Mechanically, this study proved that SNHG15 promoted OS progression via directly targeting miR-141 and negatively regulating its expression.

As a conclusion, SNHG15 could potentially be a new prognostic biomarker and therapeutic target for OS patients.

Epithelial ovarian cancer

Epithelial ovarian cancer (EOC) is a common malignant tumor in female reproductive system, accounting for 5% malignancies in female patients.⁵¹ The molecular mechanisms underlying ovarian cancer are still unclear, and the 5-year survival rate of patients at advanced stage is only 40%.⁵² Thus, there is a critical need to find effective biomarker to help early diagnosis and treatment of EOC.

Qu et al³⁰ observed that SNHG15 expression was remarkably higher in 182 EOC tissues and 6 EOC cell lines than in corresponding normal ovarian tissues and a normal cell line. Upregulated SNHG15 was notably correlated with cancer type, ascites and FIGO stage. Additionally, multivariate analysis revealed that enforced SNHG15 expression was an independent risk factor for poor overall survival and progression-free survival of EOC. Further studies verified that the abnormal expression of SNHG15 promoted proliferation, migration and invasion. Notably, SNHG15 expression was much higher in EOC cells that were cisplatin resistant than that in controls, indicating SNHG15 may contribute to the drug resistance of EOC cells.

In conclusion, SNHG15 exhibited a pivotal role in EOC progression, which may provide an opportunity for prognostic assessment and molecular target treatment in EOC patients.

Pancreatic cancer

PC remains one of the most challenging malignancies worldwide, and its incidence as well as death rate appears to be rising.^{53–55} Among all pancreatic carcinomas, pancreatic ductal adenocarcinoma (PDAC) represents around 90%. However, lack of diagnostic tests contributes to poor prognosis of PDAC.⁵⁶ So, it is necessary to explore novel biomarkers, which will contribute a crucial role in the diagnosis and therapy of PC.

Ma et al³¹ confirmed that the expression level of SNHG15 was dramatically increased in PC tissues and 3 PC cell lines. Upregulated SNHG15 was remarkably correlated with tumor size, lymph node metastasis and advanced TNM stage in PC patients. Functionally, SNHG15 knockdown attenuated cell proliferation, while induced apoptosis and alter cell cycle arrest at G0/G1 phase. Besides, silencing SNHG15 was observed to inhibit tumorigenesis *in vivo*. Mechanically, SNHG15 was observed to inhibit P15 and KLF2 expression to promote PC cell proliferation via EZH2-mediated H3K27me3.

Guo et al³² also detected that SNHG15 was overexpressed in PDAC tissues and in sera from PDAC patients compared with controls. Upregulated SNHG15 was positively associated with poor tumor differentiation, lymph node metastasis, advanced tumor stage and poorer overall survival in PDAC patients. Furthermore, Cox multivariate analyses proved that SNHG15 was an independent factor for PDAC patients' prognosis.

These data indicated that SNHG15 could serve as a biomarker for detection and prognostic prediction for PC patients.

Renal cell cancer

RCC is believed to be the most predominant form of kidney malignancies, which represents 5% of all new cancer cases in 2018 in US.² Though 5-year survival rates at diagnosis have improved, the overall prognosis for high-stage patients is still poor.⁵⁷

Du et al³³ identified that SNHG15 was remarkably upregulated in 96 RCC tissues and 5 cell lines compared with that in paired adjacent normal tissue samples and a proximal tubule epithelial cell line. Besides, upregulated SNHG15 was notably related to histological differentiation, advanced T stage and poorer survival. Knocking down SNHG15 significantly inhibited proliferation, migration, invasion and EMT process but increased apoptosis and induced cell cycle arrest at G0/

G1 phase. Furthermore, this study indicated that SNHG15 may regulate RCC progression via regulating the NF- κ B signaling pathway.

This study revealed that SNHG15 could be a new predictor of diagnosis and prognosis for RCC patients.

Thyroid cancer

Thyroid cancer is the most frequent endocrine malignant tumor and the ninth most common cancer for incidence worldwide. Though the mortality of thyroid cancer is low, the incidence of it is rising rapidly.¹ Therefore, it is imperative to explore the molecular mechanisms to provide new insight into the treatment of thyroid cancer.

Wu et al³⁴ found that SNHG15 served as an oncogene in papillary thyroid carcinoma (PTC). They indicated that the expression level of SNHG15 was higher in 92 human PTC tissues and 4 PTC cell lines than in controls. Overexpression of SNHG15 was closely associated with gender, larger tumor size, lymph node metastasis, advanced TNM stage and poorer overall survival. In addition, downregulation of SNHG15 attenuated cell proliferation, migration and EMT process but induced apoptosis in PTC cells. Mechanically, their study indicated that SNHG15 acts as a ceRNA to upregulate YAP1 signaling pathway via sponging miR-200a-3p.

However, Liu et al³⁵ concluded that SNHG15 was downregulated in 50 thyroid cancer tissues and 4 cell lines and correlated with age, pathology classification, tumor size, lymph node metastasis, clinical stage, distant metastasis and disease-free survival, indicating SNHG15 may act as an antitumor gene in thyroid cancer. This study also suggested that enhanced SNHG15 significantly suppressed proliferation, migration and invasion. Furthermore, they found that miR-510-5p promotes cell proliferation, migration and invasion via inhibiting SNHG15 in thyroid cancer.³⁶

To conclude, the function of SNHG15 varies in different studies, which may be associated with the different subtypes of thyroid cancer. Further researches are needed to confirm these findings.

Conclusion and future perspectives

Dysregulated lncRNAs has been gradually identified as potential oncogenes or tumor-suppressor genes, as these RNAs play crucial regulatory roles in tumorigenesis and progression. As a novel lncRNA, SNHG15 is widely overexpressed in multiple cancers, such as breast cancer, CRC, GC, glioma, HCC, lung cancer, OS, EOC, PC,

RCC and thyroid cancer (Figure 1). In contrast, SNHG15 is found downregulated in thyroid cancer by Liu et al. Upregulated SNHG15 was dramatically associated with multiple clinicopathological characteristics and prognosis, including TNM stage, lymph node metastasis and overall survival. In addition, SNHG15 is involved in cell proliferation, migration, invasion, apoptosis, angiogenesis, autophagy and EMT process. Mechanistically, SNHG15 could function as a ceRNA to directly interact with microRNAs (including miR-211-3p and miR-200a-3p), modifying the expression of the downstream target genes (such as SNAI1, MMP-2, MMP-9 and YAP1). SNHG15 also interacts with some proteins to modulate

gene expression. Besides, SNHG15 could regulate some classical signaling pathways contributing to cancer progression. Collectively, SNHG15 may be considered as a promising biomarker for cancer diagnosis, prognostic or therapy.

However, the molecular mechanism of SNHG15 is still unknown in several cancers, such as hepatocellular cancer and EOC. Furthermore, upstream and downstream regulation mechanisms of SNHG15 remain relatively unknown. Thus, illumination of definitive molecular mechanisms of SNHG15 will help to better understand its role on cancer progression and to provide a new direction for clinical diagnosis and treatment of tumors.

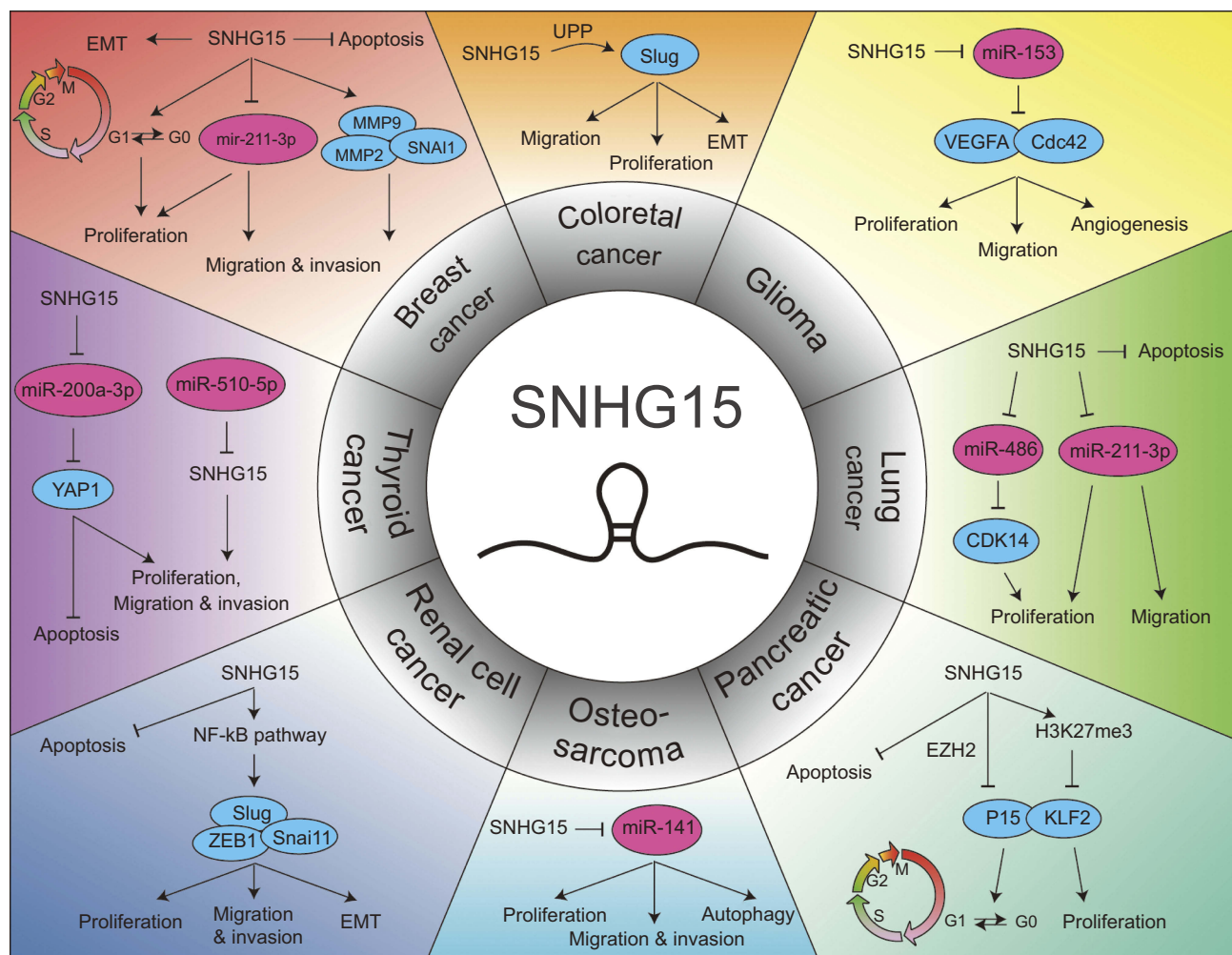


Figure 1 The molecular mechanisms of SNHG15 in different human cancers.

Abbreviations: SNHG15, small nucleolar RNA host gene 15; MALAT1, metastasis associated in lung adenocarcinoma transcript 1; ZFAS1, ZNF1 antisense RNA 1; ceRNA, competing endogenous RNA; CRC, colorectal cancer; COAD, colon adenocarcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; OS, osteosarcoma; EOC, epithelial ovarian cancer; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; PTC, papillary thyroid carcinoma; RCC, renal cell carcinoma; EMT, Epithelial to mesenchymal transition; MMP, matrix metalloproteinase; SNAI1, snail family transcriptional repressor 1; VEGFA, vascular endothelial growth factor A; CDK, cyclin-dependent kinase; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; PARP, poly(ADP-ribose) polymerase; EZH2, enhancer of zeste homolog 2.

Acknowledgments

This study was funded by the Medical and Health Research Project of Zhejiang Province (2018KY113).

Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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