Biomedicine & Pharmacotherapy 141 (2021) 111889

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

LncRNA DiGeorge syndrome critical region gene 5: A crucial regulator in malignant tumors

Haoming Xia [a], Ziyue Huang [a], Shuqiang Liu [a], Xudong Zhao [a], Risheng He [a], Zhongrui Wang [a], Wenguang Shi [a], Wangming Chen [a], Zhizhou Li [a], Liang Yu [a,b], Peng Huang [a,b], Pengcheng Kang [a], Zhilei Su [a], Yi Xu [a,b,c,*], Judy Wai Ping Yam [c,**], Yunfu Cui [a,**]

[a] Department of Hepatopancreatobiliary Surgery, The Second Affiliated Hospital of Harbin Medical University, Harbin 150086, Heilongjiang, China
[b] The key Laboratory of Myocardial Ischemia, Harbin Medical University, Ministry of Education, Harbin 150086, Heilongjiang, China
[c] Department of Pathology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 999077, Hong Kong

ARTICLE INFO

Keywords:
LncRNA
DGCR5
Regulation mechanism
Diagnostic marker
Liquid biopsy

ABSTRACT

Long non-coding RNA (lncRNA), a subgroup of ncRNA with a length of more than 200 nt without protein coding function, has been recognized by the academia for its mediating effects of dysregulated expression on the tumorigenesis and development of a variety of tumors. LncRNA DiGeorge syndrome critical region gene 5 (DGCR5), originally found to induce DiGeorge syndrome, has been confirmed to be extremely dysregulated in multiple tumors, which mediates the malignant phenotypes of hepatocellular carcinoma, pancreatic cancer, lung cancer, etc. through the regulation of Wnt/β-catenin, MEK/ERK1/2 and other cancerous signaling pathways as a molecular sponge. Researches on the cancerous derivation-related pathways involved in DGCR5 can provide potential molecular intervention targets for tumor precision treatment. Moreover, liquid biopsy based on the detection of DGCR5 in body fluids is also expected to provide a non-invasive evaluation method for the early diagnosis and prognostic evaluation of malignant tumors.

1. Introduction

The development of high-throughput sequencing technology has pushed lncRNA, the "noise" of genome transcription, to a new stage of molecular biology. More and more studies have confirmed that lncRNA can participate kinds of biological behaviors such as chromatin modification, transcription rate limiting, alternative splicing, etc. and have become potential regulatory sites for cell metabolism and cancerous derivation [1–3]. Through the research and analysis of molecular biology experimental techniques and related cancer databases, the dysregulated effect of lncRNA in diversiform tumors has been gradually confirmed, and it can be used as a potential target for early diagnosis, precise therapy and prognostic evaluation of related tumors [4,5].

DiGeorge syndrome critical region gene 5 (DGCR5) is located in human chromosomal region 22q11. It was originally used as an alternative splicing transcript without obvious protein coding ability for the DGCR region during human/mouse embryonic development. The gene serves as a disruptive site for chromosome balanced translocation and can induce changes in gene transcription in adjacent regions, thereby inducing DiGeorge syndrome [6]. With the continuous deepening of research, it has been found that DGCR5 can participate in the osteogenic differentiation of the mesenchymal stem cells in bone marrow [7], inhibiting hypoxia-induced cardiomyocyte apoptosis [8], as well as improving neuropathic pain [9]and neuronal apoptosis caused by acute spinal cord injury [10]. Furthermore, several studies in recent years have shown that DGCR5, dysregulated in a variety of tumor tissues, can

Abbreviations: BAX, BCL2 associated X, apoptosis regulator; BNIP3, BCL2 interacting protein 3; BTG1, BTG anti-proliferation factor 1; ccRCC, clear cell renal cell carcinoma; ceRNA, competing endogenous RNA; CSCs, cancer stem cells; DGCR5, DiGeorge syndrome critical region gene 5; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; EPHB6, EPH receptor B6; GEO, NCBI Gene Expression Omnibus; GSK-3β, glycogen synthase kinase 3β; KLF14, Kruppel like factor 14; lncRNA, long non-coding RNA; NSCLC, non-small cell lung carcinoma; PDAC, pancreatic ductal adenocarcinoma; PDCD4, programmed cell death 4; PTEN, phosphatase and tensin homolog; SCLC, small-cell lung carcinoma; TGF-β, transforming growth factor-β; TUSC3, tumor suppressor candidate3.

* Corresponding author at: Department of Hepatopancreatobiliary Surgery, The Second Affiliated Hospital of Harbin Medical University, Harbin 150086, Heilongjiang, China.
** Corresponding authors.
E-mail addresses: xuyihrb@hku.hk (Y. Xu), judyyam@pathology.hku.hk (J.W.P. Yam), yfcui777@hotmail.com (Y. Cui).

https://doi.org/10.1016/j.biopha.2021.111889
Received 24 April 2021; Received in revised form 30 May 2021; Accepted 28 June 2021
Available online 14 July 2021

participate in regulating the malignant biological phenotypes of tumor cells through endogenous molecular sponge effect, Wnt/β-catenin and MEK/ERK1/2 signaling pathway activation, etc. (Shown in Table 1). The continuous deepening research on it will provide guidance for the clinical monitoring and therapy of malignant tumors.

2. DGCR5 on digestive system tumors

2.1. Hepatocellular carcinoma

As the third most common cause of cancer-related deaths, hepatocellular carcinoma also ranks sixth in terms of incident cases worldwide [11]. Meanwhile, it is also the second most deadly malignant tumor after pancreatic cancer with a five-year survival rate of 18% [12], causing about one million deaths in 2030 according to the estimate of the World Health Organization [13]. Surgical resection and liver transplantation can be used for early radical treatment of HCC. However, due to the insidious nature of the onset of HCC, most patients have lost the chance of radical treatment for the advanced stage of the disease at the time of diagnosis [14]. Therefore, it is necessary to seek ideal plans for the palliative treatment of advanced HCC.

Propofol, a widely used intravenous anesthetic in clinical practice [15], has been found to exhibit excellent anti-cancer activity in multiple malignant tumors, inhibiting the invasion and metastasis, as well as inducing apoptosis of tumor cells [16–20]. Treatment with 5 μg/ml propofol for 48 h can significantly reduce the activity and induce apoptosis of HCC cells, while inhibiting the ability of metastasis and invasion, exerting active anti-cancer efficacy. The aberrant low-expression of DGCR5 in HCC pathological tissues and cell lines is confirmed by qRT-PCR. Propofol can induce the upregulation of DGCR5 in HCC cells, thereby activating its negative regulation of downstream molecules (p/t-Raf1, p/t-ERK1/2, Wnt3α, β-catenin), antagonizing the malignant biological behavior of HCC by mediating the targeted blocking of Raf1/ERK1/2 and Wnt/β-catenin signaling pathways [21]. Wang et al. [22] confirm that DGCR5 in HCC pathological tissues is significantly downregulated compared with that of adjacent normal tissues by analyzing the Oncomine database. DGCR5 exogenously upregulated by the overexpression vector can inhibit the proliferation and metastasis of tumor cells and limit the growth rate of xenograft tumors in nude mice. Mechanically, the overexpressed DGCR5 can negatively regulate β-catenin and Cyclin D1 proteins, as well as inducing the upregulation of glycogen synthase kinase 3β (GSK-3β), an inhibitor of the Wnt/β-catenin signaling pathway, thereby exerting its own tumor suppressor effect. In addition, the molecular sponge effect of DGCR5 in HCC cells is worthy of attention, which can positively regulate the expression of its downstream target, the tumor suppressor Kruppel like factor 14 (KLF14), by targeted adsorption of miR-346, and subsequently antagonizes the malignant biological phenotypes of tumor cells by mediating the synchronous expression of KLF14 [23].

2.2. Gallbladder cancer

Gallbladder cancer is a malignant tumor originating from the gallbladder epithelium, with the characteristics of high malignancy, strong infiltration, and prone to lymphatic metastasis, whose incidence accounts for 80%–95% of biliary system tumors [24,25]. According to the latest global tumor epidemiology survey, there are approximately 220,000 new gallbladder cancer patients in 2018, and more than 150,000 patients died of it [26]. Emerging clinical treatment targets and early diagnosis biomarkers will give promising results to patients with advanced gallbladder cancer.

DGCR5 in gallbladder cancer is significantly upregulated compared with that in paracancer tissues and bile duct epithelial cells. It is confirmed that exogenous silencing of DGCR5 can dramatically restrain the proliferation and metastasis of tumor cells, inducing apoptosis and cell cycle arrest, and limits the growth rate of xenograft tumors in nude mice in vivo. Mechanically, DGCR5 can competitively bind to miR-3619–5p and mediate its expression inhibition, thereby upregulating the phosphorylation level of its downstream target proteins MEK, ERK1/2, JNK, p38-MAPK without affecting the expression of proteins themselves. Therefore, MEK/ERK1/2 and JNK/p38 MAPK signaling pathways have become key channels for DGCR5 to mediate the malignant biological behaviors of gallbladder cancer cells. Notably, si-DGCR5 and the inhibitors of ERK1/2 and p38-MAPK all show ideal onco-suppressive effects in vitro and vivo, which can provide potential targets for related treatment of gallbladder cancer [27].

2.3. Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) has one of the worst prognosis of all types of cancer, whose rising incidence indicates that it will become the second most deadly malignant tumor after lung cancer in 2030 [28]. About 80% of PDAC patients have developed locally advanced or metastatic diseases at the time of initial diagnosis, and have lost the opportunity for radical tumor treatment. Combined with the clinical statistical data of each stage, the 5-year survival rate of PDAC is less than 9% [29]. Consequently, the effective screening and precise treatment strategy for PDAC will undoubtedly reduce patient's complications and improve clinical prognosis [30]. 5-FU mediates the cytotoxicity, either by interfering with the basic cell biosynthesis process by inhibiting the effect of thymidylate synthase, or by misincorporating its metabolites into RNA and DNA [31]. However, the high drug resistance of tumor cells after clinical chemotherapy has become the biggest shackle that limits its efficacy [32].

DGCR5 is extremely downregulated in the pathological tissues and cell lines of PDAC. Compared with parental cells, 5-FU resistant cells (5-FU resistant HPAC, 5-FU resistant PANC-1) cultivated with HPAC and PANC-1 cells have lower DGCR5 expression. On the one hand, si-DGCR5 can induce 5-FU resistance of HPAC/PANC-1, and on the other hand, it can further strengthen the chemotherapy resistance of 5-FU resistant HPAC/PANC-1. In terms of mechanism, DGCR5 can act as an endogenous molecular sponge to adsorb miR-320 and inhibit its expression, thereby antagonizing the negative regulation of miR-320 on the expression of its downstream target gene programmed cell death 4 (PDCD4), which involves in mediating the inhibition of proliferative, metastatic and invasive capacity, as well as epithelial-mesenchymal transition (EMT) of PDAC cells as a tumor-suppressor [33]. Similar to the results of the above studies, Li et al. [34] also reveal the regulation mechanism of DGCR5 as a molecular sponge to participate in the tumorigenesis and development of pancreatic cancer: by combining with BCL2 interacting protein 3 (BNIP3) 3′UTR, miR-27a-3p mediates the targeted inhibition of its expression. DGCR5 participates in the negative regulation of miR-27a-3p, which induces the isochronous expression with BNIP3 and further induction of the p38 phosphorylation and MAPK signaling pathway activation, thereby achieving the apoptosis of tumor cells and the growth inhibition of xenograft tumors in nude mice. Different from the above studies, Liu [35] et al. have confirmed that DGCR5 is upregulated in pancreatic cancer pathological tissues, which contributes to advanced histological grade and TNM stage, lymphatic invasion and distant metastasis. Mechanically, paired box 5 (PAX5), highly expressed in pancreatic cancer, can be used as a transcription factor to positively activate the expression of DGCR5, which can be used as a ceRNA to inhibit the expression of oncogenic factor topoisomerase 2-alpha (TOP2A) by targeting miR-3163. Upregulated TOP2A can promote the proliferation, metastasis, invasion and EMT of pancreatic cancer cells by stimulating the Wnt/β-catenin signaling pathway, as well as inhibiting the apoptosis and G0/G1 cell cycle arrest of tumor cells. Moreover, the highly expressed DGCR5 can participate in the gemcitabine resistance of pancreatic cancer, showing a severely weakened growth inhibitory effect. The above-mentioned distinct expression of DGCR5 may be attributed to the unique molecular characteristics of different pathological types of pancreatic cancer.

Table 1
The regulation mechanisms of DGCR5 on malignant tumors.

Cancer types	Clinical Samples	Assessed cancer cell lines	Expression	Related genes and pathways	Biological significance in vitro	Biological significance in vivo	Reference
Hepatocellular carcinoma	20 paired tissues	Huh-7, HepG2	Downregulated	Raf1/ERK1/2 signaling, Wnt/β-catenin signaling	Migration (-), Invasion (-), Apoptosis (+)	/	21
	225 HCC samples, 220 normal lung samples from Oncomine database	HepG2, SNU-449	Downregulated	Cyclin D1, GSK-3β, Wnt/β-catenin signaling	Migration (-), Invasion (-), Proliferation (-)	Tumor Growth (-)	22
	/	SMCC7721, Hep3B, HepG2, MHCC-97 L, MHCC-97 H, SNU449	Downregulated	miR-346/KLF14	Migration (-), Invasion (-), Proliferation (-)	/	23
Gallbladder cancer	21 paired tissues	NOZ, SGC-996, GBC-SE, OCUG	Upregulated	miR-3619–5p, MEK/ERK1/2 signaling, JNK/p38 MAPK signaling	Migration (+), Invasion (+), Proliferation (+), Apoptosis (-)	Tumor Growth (+)	27
Pancreatic cancer	30 paired tissues	PANC-1, SW1990, MIA PaCa-2, BxPC-3, HPAC	Downregulated	miR-320a/PDCD4	Migration (-), Invasion (-), Proliferation (-), EMT (-), Chemoresistance (-)	/	33
	20 paired tissues	SW1990, PANC-1	Downregulated	miR-27a-3p/BNIP3, p38, MAPK signaling	Apoptosis (+)	Tumor Growth (-)	34
	38 paired tissues	Mia PaCa-2, PuTu8988, PANC1	Upregulated	PAX5/DGCR5/miR-3163/TOP2A, Wnt/β-catenin pathway	Migration (+), Invasion (+), Proliferation (+), Apoptosis (-), EMT (+), Cell cycle arrest (-), Chemoresistance (+)	Tumor Growth (+)	35
Gastric cancer	96 paired tissues	SGC-7901, MGC-803, HGC-27, AGS	Downregulated	miR-23b/BTG1	Migration (-), Invasion (-), Proliferation (-), Apoptosis (+)	/	37
	102 paired tissues	AGS, MGC803, HGC27, SGC7901	Upregulated	/	Migration (+), Proliferation (+), Glucose uptake (+)	/	38
Laryngeal carcinoma	/	Hep-2R	Upregulated	miR-195	Proliferation (+), Radioresistance (+)	Tumor Growth (+)	44
	/	Hep-2R	Upregulated	Sxo2, Nanog, Oct4, miR-506, β-catenin, CyclinD1, GSK-3β, Wnt/β-catenin signaling	Stemness (+), Radioresistance (+)	Tumor Growth (+)	45
Lung cancer	/	A549, H460, H1299	Upregulated	Sox2, Nanog, Oct4, miR-330–5/CD44	Stemness (+)	/	50
	48 paired tissues	H520, H157, SKMES1, H460, A549, H1299	Downregulated	miR-1180, AKT, GSK-3β, β-catenin	Migration (-), Invasion (-), Proliferation (-)	/	54
	24 paired tissues	A549	Downregulated	hsa-miR-873–5p/TUSC3	Migration (-), Invasion (-), Proliferation (-), Apoptosis (+)	Tumor Growth (-)	55
	/	A549, H460, H1299	Upregulated	hsa-mir-22–3p, BAX, Cleaved-caspase-3	Proliferation (+), Apoptosis (-)	Tumor Growth (+)	51
	/	A549, H1299	Downregulated	DGCR5/miR-211–5p/EPHB6	Migration (-), Invasion (-), Proliferation (-)	Tumor Growth (-)	52
	54 paired tissues	SPCA1, H1299, PC-9, H358	Upregulated	DGCR5/miR-218–5p	Migration (+), Invasion (+)	/	53
Clear cell renal cell carcinoma	/	A498, 786-O	Upregulated	EGFR	Proliferation (+), Apoptosis (-), Cell cycle arrest (-)	Tumor Growth (+)	56
Bladder cancer	31 paired tissues	T24, 5637, SW780, RT4, UM-UC-3	Downregulated	p21, ARID1A	Migration (-), Invasion (-), Proliferation (-), Apoptosis (+), Cell cycle arrest (+)	Tumor Growth (-)	57
Prostate cancer	64 paired tissues	22Rv1, DU145	Downregulated	TGF-β	Stemness (-)	/	58
Ovarian cancer	66 paired tissues	/	Downregulated	/	/	/	61
Cervical cancer	/	MS751, SiHa, HeLa, HT-3	Downregulated	GSK-3β, Wnt/β-catenin signaling	Proliferation (-), Apoptosis (+)	Tumor Growth (-)	64
	/	HeLa, HCC94, HT-3, Caski, SiHa	Downregulated	mTOR signaling	Migration (-), Invasion (-), Proliferation (-), Apoptosis (+)	Tumor Growth (-)	65
Glioma	36 paired tissues	U251, LN229, A172, U87	Downregulated	/	Migration (-), Invasion (-), Proliferation (-), EMT (-), Apoptosis (+), Cell cycle arrest (+)	Tumor Growth (-)	66
	28 paired tissues	LN229, U251-MG, SHG44, T98G	Downregulated	NF-κB/DGCR5/miR-21/Smad7/TGFβ1 signaling, DGCR5/miR-23a/PTEN/PI3K/AKT signaling	Migration (-), Invasion (-), Proliferation (-), EMT (-), Apoptosis (+)	Tumor Growth (-)	67
	35 paired tissues		Downregulated	/	Immune activation (+)	/	68

(*continued on next page*)

Table 1 (*continued*)

Cancer types	Clinical Samples	Assessed cancer cell lines	Expression	Related genes and pathways	Biological significance in vitro	Biological significance in vivo	Reference
Triple-negative breast cancer	57 paired tissues	LN229, A172, U251, U87 MCF-7, LCC9, T-47D, SKBR3	Upregulated	Wnt3a, C-myc, Survivin, Wnt/β-catenin signaling	Migration (+), Invasion (+), Proliferation (+)	Tumor Growth (+)	69
Papillary thyroid carcinoma	519 samples	TPC1	Downregulated	miR-2861	Invasion (-), Proliferation (-)	/	70

BAX, BCL2 associated X, apoptosis regulator; BNIP3, BCL2 interacting protein 3; BTG1, BTG anti-proliferation factor 1; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; EPHB6, EPH receptor B6; GSK-3β, glycogen synthase kinase 3β; KLF14, Kruppel like factor 14; PDCD4, programmed cell death 4; PTEN, phosphatase and tensin homolog; TGF-β, transforming growth factor-β; TUSC3, tumor suppressor candidate3.

The contrasting molecular profiles that may exist in each cancer cell are worthy of further exploration; additionally, discrepancies in environmental factors may also contribute to opposite expression of DGCR5. Therefore, when using DGCR5 as a diagnostic biomarker or therapeutic target for pancreatic cancer, its specific pathological type should be prudently considered.

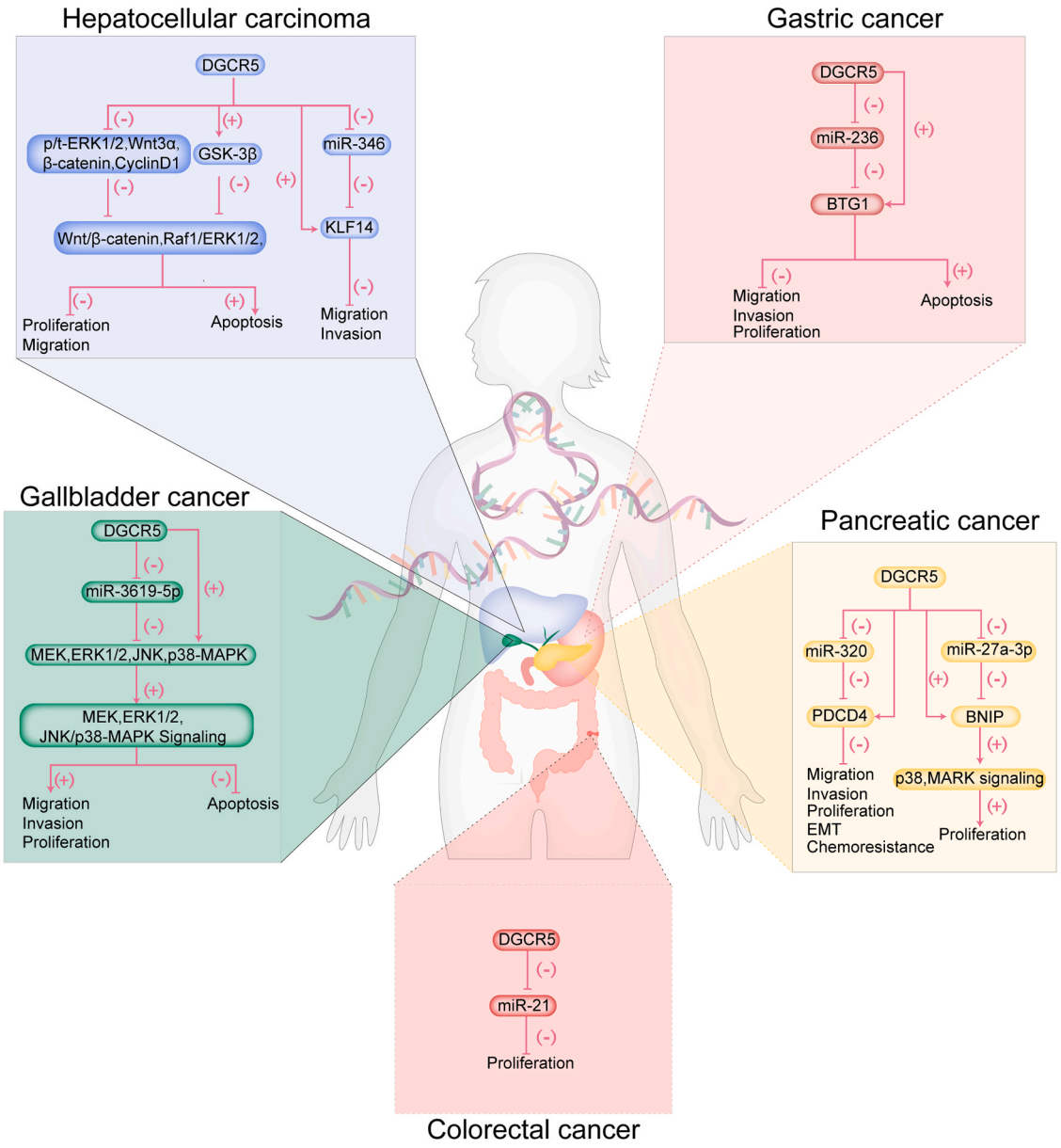

Fig. 1. The regulatory network of DGCR5 on digestive system tumors. BNIP, BCL2 interacting protein; EMT, epithelial-mesenchymal transition; DGCR5, DiGeorge syndrome critical region gene 5; GSK-3β, glycogen synthase kinase 3β; KLF14, Kruppel like factor 14; PDCD4, programmed cell death 4.

2.4. Gastric cancer

Gastric cancer is the fifth most diagnosed malignant tumor in the world, with more than one million new cases occurring every year. Meanwhile, it is also the third leading cause of cancer-related deaths attributed to the high mortality, which causing approximately 784,000 deaths worldwide in 2018 [36]. Therefore, exploring molecular biomarkers used for early diagnosis of gastric cancer and the potential therapy targets have become an urgent need to improve the clinical prognosis of patients.

DGCR5 is abnormally downregulated in the pathological tissues of gastric cancer and the plasma of patients, and its expression level is significantly correlated with tumor TNM stage, the depth of tissue invasion, and lymph node metastasis, which can be the potential predictor for early diagnosis and grade evaluation of gastric cancer. Mechanically, DGCR5, as a competing endogenous RNA (ceRNA), can mediate the derepression of its downstream target proteins phosphatase and tensin homolog (PTEN) and BTG anti-proliferation factor 1 (BTG1) by competitively binding miR-23b, thereby mediating them to exert their anti-tumor effect by antagonizing the proliferation and metastasis of tumor cells, as well as inducing apoptosis [37]. Interestingly, different from the above studies, Ni et al. [38] reveal that DGCR5 is overexpressed in gastric cancer pathological tissues, which is significantly correlated with tumor lymph node metastasis and TNM stage. Exogenous silencing of DGCR5 by siRNA can inhibit the proliferation and metastasis of gastric cancer cells, also suppressing the extracellular glucose uptake of tumor cells.

2.5. Colorectal cancer

MiR-21 is a potential participant in a variety of tumorigenesis, whose dysregulation contribute to the proliferative stimulation of tumor cells, as well as inactivating cytotoxic chemotherapeutics, such as gemcitabine, 5-FU, temozolomide, etc. Huang et al. [39] have confirmed that DGCR5 can antagonize the rapid proliferation of colorectal cancer (CRC) cells activated by overexpressed miR-21, and its expression levels are negatively correlated with advancing clinical stages. The exogenous upregulation scheme for the substantially low expression of DGCR5 in CRC will be expected to promote the treatment progress mainly based on miR-21 targeted inhibition. The regulatory network of DGCR5 on digestive system tumors is shown in Fig. 1.

3. DGCR5 on respiratory system tumors

3.1. Laryngeal carcinoma

Laryngeal carcinoma is the second most common respiratory cancer, of which squamous cell carcinoma accounts for more than 95%. Over 150,000 new cases of laryngeal carcinoma can be diagnosed each year [40], and the incidence rate has increased year by year [41]. According to statistics, there were 177,422 new cases worldwide in 2018, of which 94,771 died [27]. Radiotherapy, as a common treatment for malignant tumors, plays a vital role in reducing postoperative recurrence/metastasis and improving patient survival rate [42]. However, the high resistance of laryngeal carcinoma to radiotherapy is an important factor that impairs the efficacy [43]. Therefore, it is particularly of vital importance to identify the genes and molecular pathways involved in radiotherapy resistance.

Tang et al. [44] reveal that the highly expressed DGCR5 in the radioresistant laryngeal cancer cells Hep-2R can mediate its malignant biological behavior through the targeted expression inhibition of miR-195. Si-DGCR5 can significantly inhibit the proliferation of Hep-2R cells and enhance their radiosensitivity, as well as inhibiting the growth of xenograft tumors in nude mice in a time-dependent manner effectively. The team continues to conduct related research about the regulation of DGCR5 on Hep-2R cells phenotype in the second year: Hep-2R cells are endowed with strong CSCs-like characteristics due to their high-expression of cancer stem cells (CSCs) markers (Sxo2, Nanog, Oct4). On the one hand, knockdown of DGCR5 can enhance the radiosensitivity of Hep-2R cells. On the other hand, it can inhibit the expression of Sxo2, Nanog, Oct4, reducing the volume of Hep-2R stem cell suspended spheres and the percentage of stem-like cells. Mechanically, knocking down DGCR5 can mediate the disinhibition of its downstream molecule miR-506, and the highly expressed miR-506 can inhibit the expression of β-catenin and CyclinD1 protein, while promoting the upregulation of GSK-3β, which inducing the targeted inhibition of Wnt/β-catenin signal [45].

3.2. Lung cancer

As the most common malignant tumor worldwide, lung cancer contributes to the leading cause of cancer-related death [27]. Small-cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC), as the two main subtypes, account for 15% and 85% of all lung cancers, respectively [46]. Among them, SCLC is highly correlated with smoking, and adenocarcinoma, as a type of NSCLC, is the most common type of lung cancer, accounting for 40%–50% of all lung cancer cases [46,47]. According to statistics, the 5-year survival rate of lung cancer is only 19% [48], whose low survival rate can be attributed to 50% of NSCLC patients with metastatic disease at the time of diagnosis [49]. Therefore, reliable early diagnosis biomarkers can play a vital role in timely detection in the early stage of the disease, greatly improving the cure rate of lung cancer and patient survival; meanwhile, the targeted inhibition of the regulatory pathways of lung cancer is also the development direction of future cancer treatments.

The lung cancer cells A549 suspended spheres isolated by the stem cell spheroidization experiment shows upregulation of Sox2, Nanog, Oct4, and DGCR5 is further overexpressed compared with the parental cells. Side population cells, as a specific cell subpopulation, exhibit typical stem cell characteristics. DGCR5 can mediate the derepression of its downstream target CD44 through sponging miR-330–5p, thereby increasing the positive rate of side population cells and inducing the stem-like characteristics of lung cancer cells [50]. The overexpression of DGCR5 in pathological tissues and cell lines of lung adenocarcinoma is confirmed by Oncomine database and qRT-PCR. Si-DGCR5 can induce the positive regulation of BCL2 associated X, apoptosis regulator (BAX), cleaved-caspase-3 through upregulating hsa-mir-22–3p, then inhibits the proliferation of tumor cells and induces apoptosis, as well as suppressing the growth rate of xenograft tumors in nude mice in a time-dependent manner [51]. Similar to the above results, the studies of Kang et al. [52] and Wang et al. [53] respectively describe the mechanism of DGCR5 involving in the regulation of the tumorigenesis and development of lung cancer through DGCR5/miR-211–5p/EPH receptor B6 (EPHB6) and DGCR5/miR-218–5p axis, which provide potential targets for early diagnosis and molecular therapy of lung cancer in the future. Differently, the results of Chen et al. [54] point to the low-expression of DGCR5 in lung cancer pathological tissues and patient's serum. In terms of mechanism, DGCR5 can negatively regulate the expression of miR-1180 as a ceRNA, and antagonize the tumorigenesis and development of lung cancer by inhibiting AKT serine/threonine kinase, GSK-3β, β-catenin. Luo et al. [55] confirm that the expression of DGCR5 is significantly negatively correlated with tumor volume, lymph node metastasis and distant metastasis. The overexpressed DGCR5 can restrain the proliferative and metastatic capacity of tumor cells, as well as inducing apoptosis, while limiting the growth activity and metastasis tropism of xenograft tumors in nude mice. This study further reveals the molecular pathway of DGCR5 mediating the upregulation of tumor suppressor candidate3 (TUSC3) through the targeted suppression of hsa-miR-873–5p. The regulatory network of DGCR5 on respiratory system tumors is shown in Fig. 2.

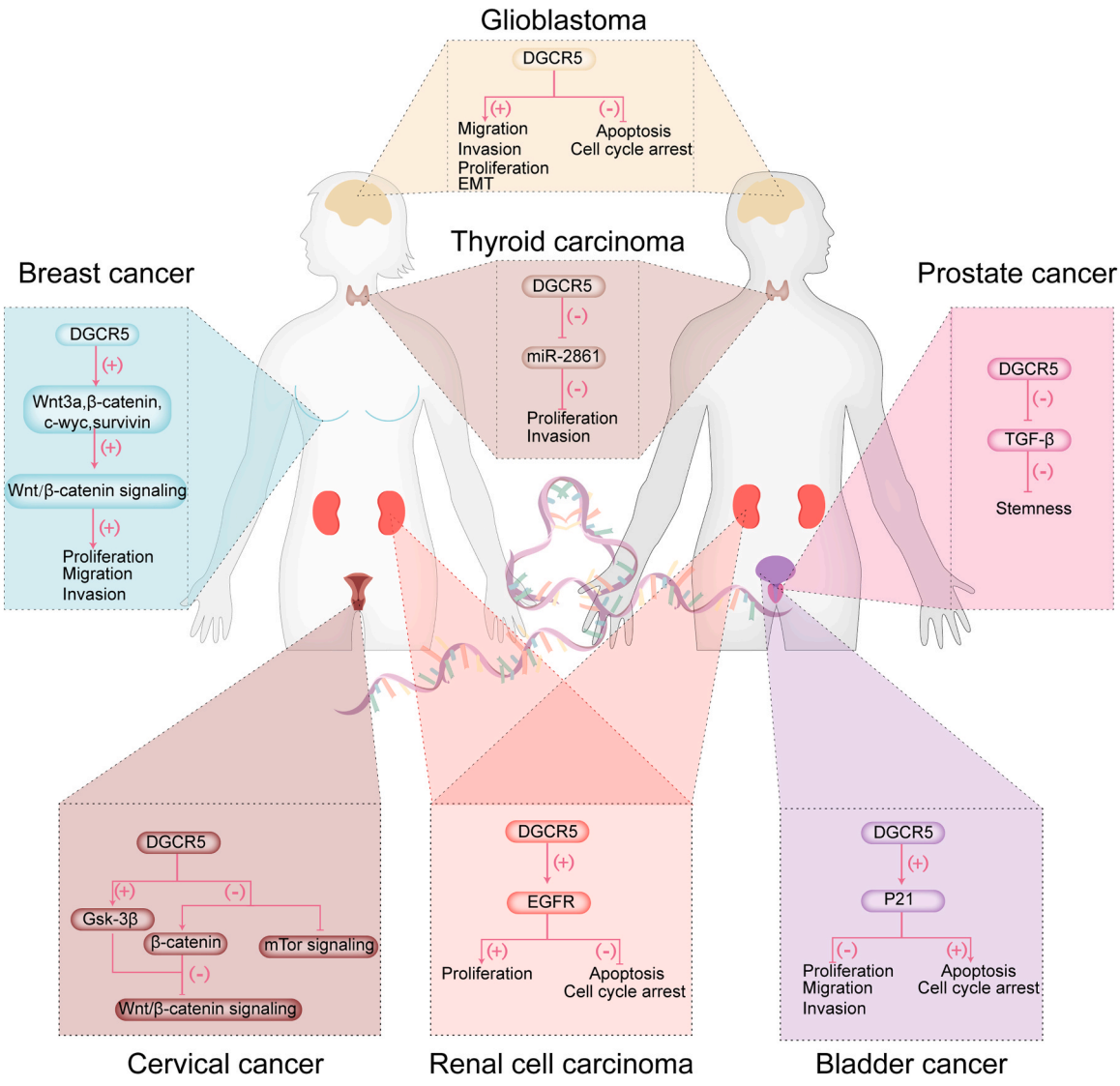

Fig. 2. The regulatory network of DGCR5 on respiratory system tumors. BAX, BCL2 associated X, apoptosis regulator; DGCR5, DiGeorge syndrome critical region gene 5; EPHB6, EPH receptor B6; GSK-3β, glycogen synthase kinase 3β.

4. DGCR5 on genitourinary system tumors

4.1. Clear cell renal cell carcinoma

Homologous analysis, LNCipedia, and HUGO Gene Nomenclature Committee and other bioinformatics techniques all point to the high-expression of DGCR5 in clear cell renal cell carcinoma (ccRCC). Exogenous silencing of DGCR5 by siRNA can inhibit the proliferation of ccRCC cells, increasing the ratio of apoptotic cells and inducing cell cycle arrest, and also exhibits a good inhibitory effect on the growth of xenograft tumors in nude mice. Further studies have confirmed that DGCR5 can participate in the expression regulation by binding to epidermal growth factor receptor (EGFR) protein at the post-translational level, but does not have a regulatory effect on EGFR mRNA [56].

4.2. Bladder cancer

DGCR5 is downregulated in bladder cancer pathological tissues and tumor cell lines. DGCR5 can mediate the proliferation, metastasis and invasion inhibition of tumor cells, also inducing apoptosis and cell cycle arrest through recruiting ARID1A in the p21 promoter region to activate its mRNA transcription. Meanwhile, the xenograft tumors of nude mice in the DGCR5 ectopic expression group show a remarkable growth inhibitory effect compared to the control group [57].

4.3. Prostate cancer

The expression of DGCR5 in the pathological tissues of prostate cancer is observably lower than that in the adjacent normal tissues, and the 5-year overall survival rate of patients with DGCR5 low-expression is markedly reduced. In vitro, overexpressed DGCR5 can inhibit the mRNA and protein expression of its downstream target transforming growth factor-β (TGF-β), while reducing the percentage of prostate cancer stem cells (CD133 +) [58].

4.4. Ovarian cancer

Ovarian cancer is not only the seventh most common cancer among women worldwide, but also the second most common malignancy after breast cancer among women over 40 [59]. Although the survival rate has improved in recent decades, two-thirds of patients still die within 10 years after diagnosis, and the 5-year survival rate of patients with advanced invasive epithelial ovarian cancer is less than 20% [60].

Consequently, the increase in the early diagnosis rate of ovarian cancer shows vital importance.

It is confirmed by qRT-PCR and NCBI Gene Expression Omnibus (GEO) database that DGCR5 is signally downregulated in the pathological tissues of ovarian cancer compared to adjacent normal tissues, and the expression of DGCR5 in ovarian cancer patients with lymph node and/or distant metastatic is further downregulated compared with patients without metastasis, which is also significantly related to tumor volume, TNM stage, lymph node and distant metastasis [61].

4.5. Cervical cancer

Cervical cancer is one of the fourth most common cancer in women worldwide [62], with 530,000 new cases and 270,000 deaths estimated each year. Although surgery is the standard treatment for early cervical cancer, the prognosis is poor due to the high recurrence rate of cervical cancer [63]. Therefore, it is urgent to find molecular targets for adjuvant surgical treatment and assessment of patient prognosis.

The expression level of DGCR5 in cervical cancer cells is significantly lower than that in cervical epithelial cells. Overexpressed DGCR5 can mediate the positive regulation of GSK-3β and the low-expression of β-catenin to achieve Wnt signaling pathway targeted inhibition, thereby suppressing the proliferation capacity of tumor cells and inducing apoptosis [64]. Similar to the findings of the above study, Yuan et al. [65] demonstrate the activation effect of downregulated DGCR5 in cervical cancer cells on the mTOR signaling pathway in vivo and vitro, suggesting that it can be taken advantaged as a potential target for early diagnosis and molecular therapy of cervical cancer and prognostic evaluation.

5. DGCR5 on other tumors

5.1. Glioma

DGCR5 is extremely downregulated in Glioblastoma pathological tissues and tumor cell lines. Exogenously upregulating the expression of DGCR5 can suppress the viability, metastasis, invasion and EMT of tumor cells, as well as inducing G0/G1 cell cycle arrest and apoptosis, meanwhile performing a significant inhibitory effect on the growth of xenograft tumors in nude mice [66]. DGCR5 is extremely downregulated in glioma relative to adjacent tissues, whose expression level is negatively correlated with histological stage. As a common transcription factor, NF-κB participates in mediating crucial characteristics related to mesenchymal differentiation, as well as targeting the DGCR5 promoter to inhibit its expression. DGCR5 is a tumor suppressor in glioma to antagonize the malignant biological behaviors of tumors: on the one hand, DGCR5 can be used as a molecular sponge to target miR-21, thereby liberating its downstream target Smad7, which restrains the metastasis, invasion and EMT of tumor cells by inhibiting TGFβ1 signaling; on the other hand, DGCR5 can upregulate PTEN by adsorbing miR-23a. PTEN can suppress the activation of PI3K/AKT signaling through lipid phosphatase activity, thereby inhibiting the proliferation of glioma cells, as well as inducing apoptosis and slowing down the growth of xenografts in nude mice in vivo [67]. IDH mutation status contributes to the clinical outcome of glioma patients. The prognosis of IDH mutant glioma is significantly better than IDH wild-type glioma with similar grade. Wu [68] et al. have verified that compared with the downregulated DGCR5 in IDH wild-type glioma, DGCR5 is enriched in IDH mutant glioma. Consequently, DGCR5 can be taken advantaged as a biomarker for distinguishing IDH status in glioma, with the AUC in the TCGA and CGGA database are 71.4% and 69.4%, respectively. Further, DGCR5 is enriched in immune-related pathways, whose expression is negatively related to the majority of myeloid cells and stromal cells, and positively correlated with anti-tumor cells such as CD8 + T cells, mesenchymal stem cells and eosinophils, suggesting the noteworthy influence of DGCR5 upon the infiltration of stromal cells and immune cells in the tumor microenvironment. Furthermore, DGCR5 has also been confirmed to negatively interact with the immune checkpoints in glioma, including PD-1 (PDCD1), PD-L1 (CD274) and CTLA-4, et al., as well as the majority of immunosuppressive cell recruitment factors (tumor-associated neutrophils, recruit myeloid-derived suppressor cells, and tumor-associated macrophages).

5.2. Triple-negative breast cancer

The expression level of DGCR5 is positively related to the TNM stage and lymph node metastasis of triple-negative breast cancer. Si-DGCR5 can inhibit the Wnt/β-catenin signaling pathway by negatively regulating the expression of Wnt3a, β-catenin, C-myc and Survivin proteins, thereby inhibiting the proliferation, migration and invasion of tumor cells, as well as limiting the growth rate of xenograft tumors in nude mice and reducing the number of liver and lung metastasis nodules in vivo [69].

5.3. Papillary thyroid carcinoma

In addition to confirming the aberrant low-expression of DGCR5 in the pathological tissues and tumor cell lines of papillary thyroid carcinoma by qRT-PCT, Chen et al. [70] also reveal the potential mechanism of DGCR5 to inhibit tumor cell proliferation and invasion by negatively regulating the expression of its downstream target miR-2861. The regulatory network of DGCR5 on other malignant tumors is shown in Fig. 3.

6. The diagnostic or prognostic value of dysregulated DGCR5

Owing to the insidious early onset and the inconspicuous clinical symptoms of malignant tumors, most patients are in the advanced stage of the disease at diagnosis, losing the opportunity for radical resection. Existing inspection methods, including MRI, enhanced CT, ultrasound and molecular pathology testing, are subject to economic burden and invasiveness, making it difficult to universally apply. Likewise, current biomarkers show poor diagnostic results due to the lack of sufficient sensitivity and specificity. In view of the mediation of dysregulated lncRNA on cancer-related pathways, abnormally expressed lncRNAs can be identified in tumor cells or biological fluids (such as serum, urine, saliva, etc.) as biomarkers for the diagnosis and prognosis of malignant tumors [71]. Growing evidences have confirmed that lncRNA PCA3 (prostate cancer antigen 3) can be overexpressed by 60- to 100-fold in more than 90% of prostates and is undetectable in other tumor types [72–74]. Urinary PCA3 as a diagnostic biomarker has shown superior diagnostic efficacy to serum prostate specific antigen (PSA) and digital rectal examination, with a sensitivity of 58–82% and a specificity of 56–76% [75]. Nowadays, urine PCA3 is widely used in prostate cancer detection and has been approved by the US Food and Drug Administration (FDA) [76]. Therefore, lncRNA-based liquid biopsy, as an emerging non-invasive examination method, has shown ideal diagnostic and prognostic evaluation in many studies, which is expected to provide more detailed and personalized decision-making for cancer management.

DGCR5 in HCC is notably related to cancer specific survival (CSS), and the 5-year survival rate of patients with low expression is lower than that of the high expression group (10.3% vs 36.6%). Juxtaposed with larger tumor and poor/undifferentiated grade, the low expression of DGCR5 is considered an important risk factor for poor prognosis according to univariate analysis. Multivariate analysis points to Edmondson grade and DGCR5 as independent predictors of HCC prognosis. Additionally, DGCR5 can be used as an effective predictor to diagnose early HCC (AUC=0.782; sensitivity=0.633, specificity=0.833) [77]. The median survival of PDAC patients in the DGCR high-expression group was significantly better than that in the low-expression group (847days vs 541days), indicating the crucial value of DGCR5 in the prognostic evaluation of PDAC. According to the ROC curve analysis,

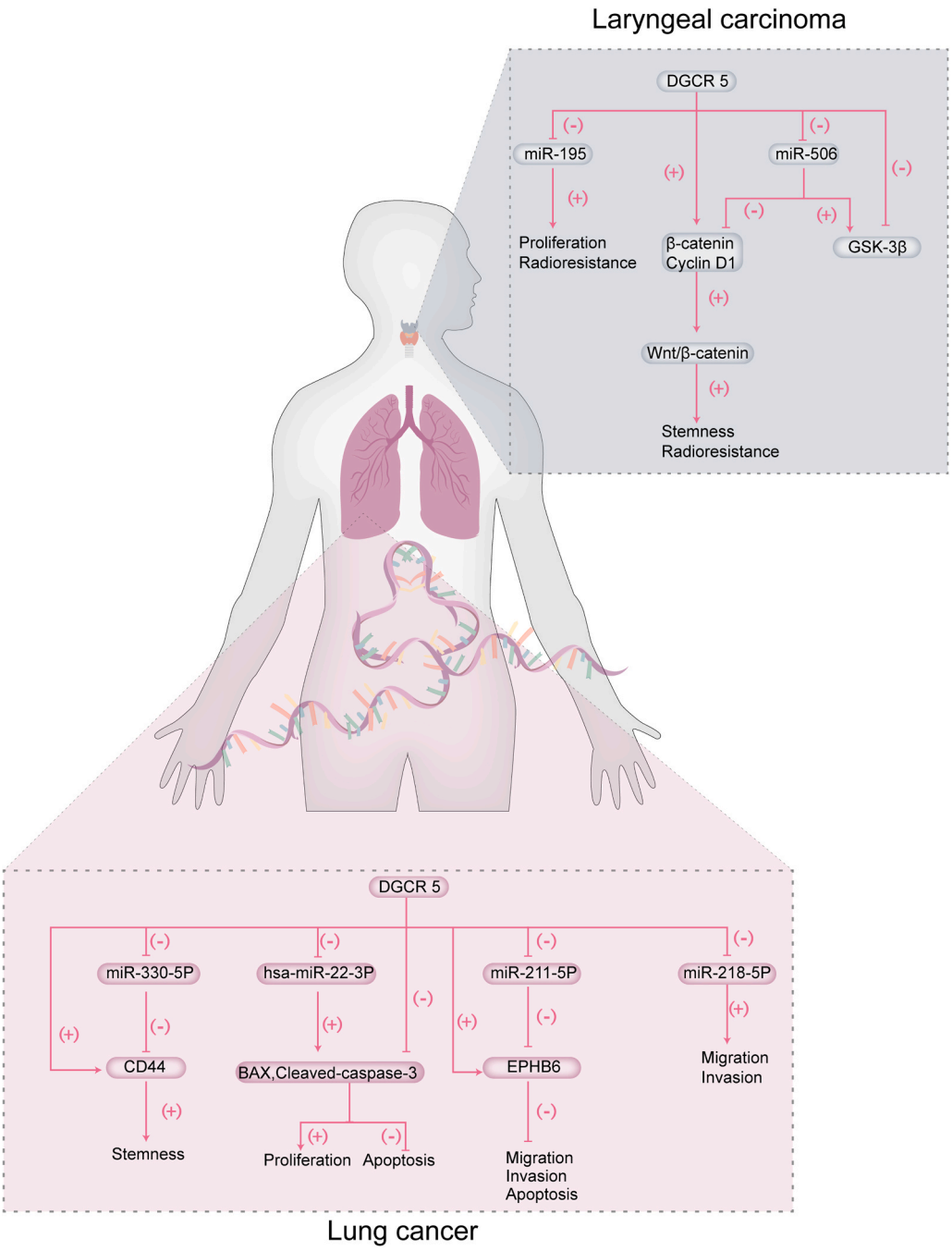

Fig. 3. The regulatory network of DGCR5 on other tumors. DGCR5, DiGeorge syndrome critical region gene 5; EGFR, epidermal growth factor receptor; GSK-3β, glycogen synthase kinase 3β; TGF-β, transforming growth factor-β.

DGCR5 can also be used as a predictor of early diagnosis of PDAC (AUC=0.735) [33]. Conversely, Liu et al. [35] have demonstrated that pancreatic cancer patients with high DGCR5 expression have poorer OS. DGCR5 expression can be used as an independent risk factor and negatively correlates with the prognosis of pancreatic cancer patients. Additionally, DGCR5 not only shows ideal early diagnosis effect in gastric cancer [37] and laryngeal squamous cell carcinoma [78] (AUC=0.722, 0.721, respectively), it can also be used as a potential predictor for grading evaluation. The level of serum DGCR5 in patients with lung cancer after surgery is significantly higher than that before surgery. Kaplan-Meier survival analysis shows that upregulated DGCR5 predicts a relatively longer overall survival [54]. The expression of DGCR5 in patients with ovarian cancer accompanied by lymph node metastasis and/or distant metastasis is further downregulated compared with patients without metastasis. The overall survival of patients in the low-expression group of DGCR5 is significantly poorer than that in the high-expression group. Univariate and multivariate analysis have confirmed that DGCR5 can be used as an independent predictor of poor prognosis in ovarian cancer patients, juxtaposed with lymph node metastasis, distant metastasis and clinical stage. Moreover, DGCR5 can be used to distinguish ovarian cancer tissues from adjacent tissues (AUC=0.876), with or without lymph node metastasis (AUC=0.819), good overall survival or poor overall survival (AUC=0.692), indicating that DGCR5 has potential evaluation value for the early diagnosis and prognosis of ovarian cancer [61].

7. Conclusions

The development of high-throughput sequencing technology has pushed lncRNA to a new horizon. Various pathophysiological regulatory mechanisms, including DNA methylation, histone modification, and nuclear transport, etc. are gradually being explored by the academia. Additionally, numerous studies have shown that the dysregulated lncRNA shows elaborate regulatory effect on the tumorigenesis and development of malignant tumors. DGCR5, as a member of the lncRNA family, has been found dysregulated in kinds of high-incidence malignant tumors such as liver cancer, gastric cancer, lung cancer and breast cancer, etc. It can participate in the regulation of malignant phenotype of tumor cells through various mechanisms such as endogenous molecular sponge, Wnt/β-catenin and MEK/ERK1/2 signal pathway activation. Meanwhile, clinicopathological analysis of different tumors points to a tight correlation between the expression level of DGCR5 and the prognosis of patients, indicating that DGCR5 can be used as a potential molecular therapy target for tumors and a biological marker for early diagnosis and prognostic evaluation. However, there are still many problems that need to be solved urgently behind the basic experiments. Firstly, the actual regulatory effect of DGCR5 in cells or animals is difficult to replicate in a complex human environment, and its anticancer effect by upregulation/downregulation needs to be further confirmed. Secondly, the in vivo delivery vector for therapeutic lncRNA has not been found yet, and it is tough to prevent lncRNA from being inactivated by the immune system. Thirdly, the related research of DGCR5 is still in its infancy, and the instigator of its dysregulation and the specific downstream molecular regulatory network need to be further explored. In summary, despite the many challenges, basic research on DGCR5 has shown good results, and it is expected to achieve breakthroughs in clinical trials in the future, which will bring hope to the diagnosis, treatment and prognosis evaluation of patients with malignant tumors.

CRediT authorship contribution statement

Haoming Xia: Conceptualization, Writing - original draft, Writing - review & editing. **Ziyue Huang:** Conceptualization. **Shuqiang Liu:** Validation. **Xudong Zhao:** Validation, Writing - original draft. **Risheng He:** Writing - original draft. **Zhongrui Wang:** Writing - original draft. **Wenguang Shi:** Writing - original draft. **Wangming Chen:** Writing - review & editing. **Zhizhou Li:** Writing - review & editing. **Liang Yu:** Visualization. **Peng Huang:** Visualization. **Pengcheng Kang:** Supervision. **Zhilei Su:** Supervision. **Yi Xu:** Project administration, Funding acquisition. **Judy Wai Ping Yam:** Project administration. **Yunfu Cui:** Project administration, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgments

This work was supported by National Natural Science Foundation of China, [grant numbers 81902431]; China Postdoctoral Science Foundation, [grant numbers 2019T120279, 2018M641849]; Foundation of Key Laboratory of Myocardial Ischemia, Ministry of Education, [grant numbers KF201810]; Heilongjiang Postdoctoral Science Foundation, [grant numbers LBH-Z18107]; Out-standing Youth Project of Natural Science Foundation of Heilongjiang, [grant numbers YQ2019H007]; and Hong Kong Scholars Program, [grant numbers XJ2020012].

References

[1] F. Kopp, J.T. Mendell, Functional classification and experimental dissection of long noncoding RNAs, Cell 172 (2018) 393–407, https://doi.org/10.1016/j.cell.2018.01.011. PMID: 29373828.
[2] M. Fabbri, L. Girnita, G. Varani, G.A. Calin, Decrypting noncoding RNA interactions, structures, and functional networks, Genome Res 29 (2019) 1377–1388, https://doi.org/10.1101/gr.247239.118. PMID: 31434680.
[3] E. Anastasiadou, L.S. Jacob, F.J. Slack, Non-coding RNA networks in cancer, Nat. Rev. Cancer 18 (2018) 5–18, https://doi.org/10.1038/nrc.2017.99. PMID: 29170536.
[4] L. Statello, C.J. Guo, L.L. Chen, M. Huarte, Gene regulation by long non-coding RNAs and its biological functions, Nat. Rev. Mol. Cell Biol. 22 (2021) 96–118, https://doi.org/10.1038/s41580-020-00315-9. PMID: 33353982.
[5] S. Chen, X. Shen, Long noncoding RNAs: functions and mechanisms in colon cancer, Mol. Cancer 19 (2020) 167, https://doi.org/10.1186/s12943-020-01287-2. PMID: 33246471.
[6] H.F. Sutherland, R. Wadey, J.M. McKie, C. Taylor, U. Atif, K.A. Johnstone, S. Halford, U.J. Kim, J. Goodship, A. Baldini, P.J. Scambler, Identification of a novel transcript disrupted by a balanced translocation associated with DiGeorge syndrome, Am. J. Hum. Genet 59 (1996) 23–31. PMID: 8659529.
[7] Z.H. Wu, K.H. Huang, K. Liu, G.T. Wang, Q. Sun, DGCR5 induces osteogenic differentiation by up-regulating Runx2 through miR-30d-5p, Biochem Biophys. Res Commun. 505 (2018) 426–431, https://doi.org/10.1016/j.bbrc.2018.09.033. PMID: 30266402.
[8] J. Dai, J. Ma, Y. Liao, X. Luo, G. Chen, Polydatin protects H9c2 cells from hypoxia-induced injury via up-regulating long non-coding RNA DGCR5, Braz. J. Med Biol. Res 52 (2019) 8834, https://doi.org/10.1590/1414-431×20198834. PMID: 31826181.
[9] C. Peng, C. Zhang, Z. Su, D. Lin, DGCR5 attenuates neuropathic pain through sponging miR-330-3p and regulating PDCD4 in CCI rat models, J. Cell Physiol. 234 (2019) 7292–7300, https://doi.org/10.1002/jcp.27487. PMID: 30317600.
[10] H. Zhang, W. Wang, N. Li, P. Li, M. Liu, J. Pan, D. Wang, J. Li, Y. Xiong, L. Xia, LncRNA DGCR5 suppresses neuronal apoptosis to improve acute spinal cord injury through targeting PRDM5, Cell Cycle 17 (2018) 1992–2000, https://doi.org/10.1080/15384101.2018.1509622. PMID: 30146926.
[11] A. Forner, M. Reig, J. Bruix, Hepatocellular carcinoma, Lancet 391 (2018) 1301–1314, https://doi.org/10.1016/S0140-6736(18)30010-2. PMID: 29307467.
[12] A. Jemal, E.M. Ward, C.J. Johnson, K.A. Cronin, J. Ma, B. Ryerson, A. Mariotto, A. J. Lake, R. Wilson, R.L. Sherman, R.N. Anderson, S.J. Henley, B.A. Kohler, L. Penberthy, E.J. Feuer, H.K. Weir, Annual report to the nation on the status of cancer, 1975-2014, featuring survival, J. Natl. Cancer Inst. 109 (2017) djx030, https://doi.org/10.1093/jnci/djx030. PMID: 28376154.
[13] A. Villanueva, Hepatocellular carcinoma, N. Engl. J. Med. 380 (2019) 1450–1462, https://doi.org/10.1056/NEJMra1713263. PMID: 30970190.
[14] A. Forner, M. Reig, J. Bruix, Hepatocellular carcinoma, Lancet 391 (2018) 1301–1314, https://doi.org/10.1016/S0140-6736(18)30010-2. PMID: 29307467.
[15] M.M. Sahinovic, M.M.R.F. Struys, A.R. Absalom, Clinical pharmacokinetics and pharmacodynamics of propofol, Clin. Pharm. 57 (2018) 1539–1558, https://doi.org/10.1007/s40262-018-0672-3. PMID: 30019172.
[16] Y. Miao, Y. Zhang, H. Wan, L. Chen, F. Wang, GABA-receptor agonist, propofol inhibits invasion of colon carcinoma cells, Biomed. Pharm. 64 (2010) 583–588, https://doi.org/10.1016/j.biopha.2010.03.006. PMID: 20888181.
[17] Q. Li, L. Zhang, Y. Han, Z. Jiang, Q. Wang, Propofol reduces MMPs expression by inhibiting NF-κB activity in human MDA-MB-231 cells, Biomed. Pharm. 66 (2012) 52–56, https://doi.org/10.1016/j.biopha.2011.10.006. PMID: 22264881.
[18] K.C. Wu, S.T. Yang, T.C. Hsia, J.S. Yang, S.M. Chiou, C.C. Lu, R.S. Wu, J.G. Chung, Suppression of cell invasion and migration by propofol are involved in down-regulating matrix metalloproteinase-2 and p38 MAPK signaling in A549 human lung adenocarcinoma epithelial cells, Anticancer Res. 32 (2012) 4833–4842. PMID: 23155249.
[19] J. Zhang, D. Zhang, G.Q. Wu, Z.Y. Feng, S.M. Zhu, Propofol inhibits the adhesion of hepatocellular carcinoma cells by upregulating microRNA-199a and downregulating MMP-9 expression, Hepatobiliary Pancreat. Dis. Int. 12 (2013) 305–309, https://doi.org/10.1016/s1499-3872(13)60048-x. PMID: 23742776.
[20] F. Zhang, C. Wang, Y. Cui, S. Li, Y. Yao, Y. Ci, J. Wang, W. Hou, A. Wu, E. Li, Effects of propofol on several membrane characteristics of cervical cancer cell lines, Cell Physiol. Biochem 40 (2016) 172–182, https://doi.org/10.1159/000452535. PMID: 27855373.
[21] Y. Sun, H. Sun, Propofol exerts anticancer activity on hepatocellular carcinoma cells by raising lncRNA DGCR5, J. Cell Physiol. 235 (2020) 2963–2972, https://doi.org/10.1002/jcp.29202. PMID: 31538334.
[22] X.L. Wang, M. Shi, T. Xiang, Y.Z. Bu, Long noncoding RNA DGCR5 represses hepatocellular carcinoma progression by inactivating Wnt signaling pathway, J. Cell Biochem. 120 (2019) 275–282, https://doi.org/10.1002/jcb.27342.
[23] Y.G. Wang, J. Liu, M. Shi, F.X. Chen, LncRNA DGCR5 represses the development of hepatocellular carcinoma by targeting the miR-346/KLF14 axis, J. Cell Physiol. 234 (2018) 572–580, https://doi.org/10.1002/jcp.26779.
[24] T.O. Goetze, Gallbladder carcinoma: prognostic factors and therapeutic options, World J. Gastroenterol. 21 (2015) 12211–12217, https://doi.org/10.3748/wjg.v21.i43.12211.
[25] S.H. Wang, X.C. Wu, M.D. Zhang, M.Z. Weng, D. Zhou, Z.W. Quan, Upregulation of H19 indicates a poor prognosis in gallbladder carcinoma and promotes epithelial-mesenchymal transition, Am. J. Cancer Res. 6 (2015) 15–26.
[26] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36

cancers in 185 countries, CA Cancer J. Clin. 68 (2018) 394–424, https://doi.org/10.3322/caac.21492.
[27] S. Liu, B. Chu, C. Cai, X. Wu, W. Yao, Z. Wu, Z. Yang, F. Li, Y. Liu, P. Dong, W. Gong, DGCR5 promotes gallbladder cancer by sponging MiR-3619-5p via MEK/ERK1/2 and JNK/p38 MAPK Pathways, J. Cancer 11 (2020) 5466–5477, https://doi.org/10.7150/jca.46351.
[28] L. Rahib, B.D. Smith, R. Aizenberg, A.B. Rosenzweig, J.M. Fleshman, L. M. Matrisian, Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States, Cancer Res. 74 (2014) 2913–2921, https://doi.org/10.1158/0008-5472.CAN-14-0155.
[29] C. Nevala-Plagemann, M. Hidalgo, I. Garrido-Laguna, From state-of-the-art treatments to novel therapies for advanced-stage pancreatic cancer, Nat. Rev. Clin. Oncol. 17 (2020) 108–123, https://doi.org/10.1038/s41571-019-0281-6.
[30] J. Kleeff, M. Korc, M. Apte, La Vecchia, C.D. Johnson, A.V. Biankin, R.E. Neale, M. Tempero, D.A. Tuveson, R.H. Hruban, J.P. Neoptolemos, Pancreatic cancer, Nat. Rev. Dis. Prim. 2 (2016) 16022, https://doi.org/10.1038/nrdp.2016.22.
[31] D.B. Longley, D.P. Harkin, P.G. Johnston, 5-fluorouracil: mechanisms of action and clinical strategies, Nat. Rev. Cancer 3 (2003) 330–338, https://doi.org/10.1038/nrc1074.
[32] J. Gu, Z. Li, J. Zhou, Z. Sun, C. Bai, Response prediction to oxaliplatin plus 5-fluorouracil chemotherapy in patients with colorectal cancer using a four-protein immunohistochemical model, Oncol. Lett. 18 (2019) 2091–2101, https://doi.org/10.3892/ol.2019.10474.
[33] S. Yong, Y. Yabin, Z. Bing, Z. Chuanrong, G. Dianhua, Z. Jianhuai, Y. Weidong, W. Shuming, L. Ling, Reciprocal regulation of DGCR5 and miR-320a affects the cellular malignant phenotype and 5-FU response in pancreatic ductal adenocarcinoma, Oncotarget 8 (2017) 90868–90878, https://doi.org/10.18632/oncotarget.18377.
[34] X. Li, S. Zhou, T. Fan, X. Feng, lncRNA DGCR 5/miR-27a-3p/BNIP3 promotes cell apoptosis in pancreatic cancer by regulating the p38 MAPK pathway, Int J. Mol. Med 46 (2020) 729–739, https://doi.org/10.3892/ijmm.2020.4632.
[35] S.L. Liu, C. Cai, Z.Y. Yang, Z.Y. Wu, X.S. Wu, X.F. Wang, P. Dong, W. Gong, DGCR5 is activated by PAX5 and promotes pancreatic cancer via targeting miR-3163/TOP2A and activating Wnt/β-catenin pathway, Int. J. Biol. Sci. 17 (2021) 498–513, https://doi.org/10.7150/ijbs.55636.
[36] E.C. Smyth, M. Nilsson, H.I. Grabsch, N.C. van Grieken, F. Lordick, Gastric cancer, Lancet 396 (2020) 635–648, https://doi.org/10.1016/S0140-6736(20)31288-5.
[37] Y. Xu, G. Zhang, C. Zou, Z. Gong, S. Wang, J. Liu, G. Ma, X. Liu, W. Zhang, P. Jiang, Long noncoding RNA DGCR5 suppresses gastric cancer progression by acting as a competing endogenous RNA of PTEN and BTG1, J. Cell Physiol. 234 (2019) 11999–12010, https://doi.org/10.1002/jcp.27861.
[38] C. Ni, P. Yang, J. Guo, M. Ye, Role of DiGeorge syndrome critical region gene 9, a long noncoding RNA, in gastric cancer, Onco Targets Ther. 11 (2018) 2259–2267, https://doi.org/10.2147/OTT.S162253.
[39] H. Huang, X. Yang, J. Chen, J. Fu, C. Chen, J. Wen, Q. Mo, lncRNA DGCR5 inhibits the proliferation of colorectal cancer cells by downregulating miR-21, Oncol. Lett. 18 (2019) 3331–3336, https://doi.org/10.3892/ol.2019.10671.
[40] V. Calkovsky, P. Wallenfels, A. Calkovska, A. Hajtman, Laryngeal cancer: 12-year experience of a single center, Adv. Exp. Med Biol. 911 (2016) 9–16, https://doi.org/10.1007/5584_2015_201.
[41] A. Jemal, R. Siegel, J. Xu, E. Ward, Cancer statistics, 2010, CA Cancer J. Clin. 60 (2010) 277–300, https://doi.org/10.3322/caac.20073.
[42] A.I. Ghanem, M. Schymick, S. Bachiri, A. Mannari, J. Sheqwara, C. Burmeister, S. Chang, T. Ghanem, F. Siddiqui, The effect of treatment package time in head and neck cancer patients treated with adjuvant radiotherapy and concurrent systemic therapy, World J. Otorhinolaryngol. Head. Neck Surg. 5 (2019) 160–167, https://doi.org/10.1016/j.wjorl.2018.09.005.
[43] F. Perri, R. Pacelli, G.D.V. Scarpati, L. Cella, M. Giuliano, F. Caponigro, S. Pepe, Radioresistance in head and neck squamous cell carcinoma: biological bases and therapeutic implications, Head Neck 37 (5) (2015) 763–770.
[44] T. Tang, G. Shan, F. Zeng, Knockdown of DGCR5 enhances the radiosensitivity of human laryngeal carcinoma cells via inducing miR-195, J. Cell Physiol. 234 (2019) 12918–12925, https://doi.org/10.1002/jcp.27958.
[45] T. Tang, G. Shan, DGCR5 promotes cancer stem cell-like properties of radioresistant laryngeal carcinoma cells by sponging miR-506 via Wnt pathway, J. Cell Physiol. 234 (2019) 18423–18431, https://doi.org/10.1002/jcp.28478.
[46] C. Zappa, S.A. Mousa, Non-small cell lung cancer: current treatment and future advances, Transl. Lung Cancer Res 5 (2016) 288–300, https://doi.org/10.21037/tlcr.2016.06.07.
[47] S. Couraud, G. Zalcman, B. Milleron, F. Morin, P.J. Souquet, Lung cancer in never smokers–a review, Eur. J. Cancer 48 (2012) 1299–1311, https://doi.org/10.1016/j.ejca.2012.03.007.
[48] B.C. Bade, Dela, C.S. Cruz, Lung cancer 2020: epidemiology, etiology, and prevention, Clin. Chest Med. 41 (2020) 1–24, https://doi.org/10.1016/j.ccm.2019.10.001.
[49] V.W. Chen, B.A. Ruiz, M.C. Hsieh, X.C. Wu, L.A. Ries, D.R. Lewis, Analysis of stage and clinical/prognostic factors for lung cancer from SEER registries: AJCC staging and collaborative stage data collection system, Cancer 120 (2014) 3781–3792, https://doi.org/10.1002/cncr.29045.
[50] R. Wang, H.X. Dong, J. Zeng, J. Pan, X.Y. Jin, LncRNA DGCR5 contributes to CSC-like properties via modulating miR-330-5p/CD44 in NSCLC, J. Cell Physiol. 233 (2018) 7447–7456, https://doi.org/10.1002/jcp.26590.
[51] H.X. Dong, R. Wang, X.Y. Jin, J. Zeng, J. Pan, LncRNA DGCR5 promotes lung adenocarcinoma (LUAD) progression via inhibiting hsa-mir-22-3p, J. Cell Physiol. 233 (2018) 4126–4136, https://doi.org/10.1002/jcp.26215.
[52] M. Kang, J. Shi, B. Li, M. Luo, S. Xu, X. Liu, LncRNA DGCR5 regulates the non-small cell lung cancer cell growth, migration, and invasion through regulating miR-211-5p/EPHB6 axis, Biofactors 45 (2019) 788–794, https://doi.org/10.1002/biof.1539.
[53] J. Wang, H.Z. Shu, C.Y. Xu, S.G. Guo, LncRNA DGCR5 promotes non-small cell lung cancer progression via sponging miR-218-5p, Eur. Rev. Med. Pharm. Sci. 23 (2019) 9947–9954, https://doi.org/10.26355/eurrev_201911_19561.
[54] E.G. Chen, J.S. Zhang, S. Xu, X.J. Zhu, H.H. Hu, Long non-coding RNA DGCR5 is involved in the regulation of proliferation, migration and invasion of lung cancer by targeting miR-1180, Am. J. Cancer Res. 7 (2017) 1463–1475.
[55] J. Luo, H. Zhu, H. Jiang, Y. Cui, M. Wang, X. Ni, C. Ma, The effects of aberrant expression of LncRNA DGCR5/miR-873-5p/TUSC3 in lung cancer cell progression, Cancer Med. 7 (2018) 3331–3341, https://doi.org/10.1002/cam4.1566.
[56] X. Gong, X. Du, Y. Xu, W. Zheng, LINC00037 inhibits proliferation of renal cell carcinoma cells in an epidermal growth factor receptor-dependent way, Cell Physiol. Biochem. 45 (2018) 523–536, https://doi.org/10.1159/000487030.
[57] C. Fang, W. He, T. Xu, J. Dai, L. Xu, F. Sun, Upregulation of lncRNA DGCR5 correlates with better prognosis and inhibits bladder cancer progression via transcriptionally facilitating P21 expression, J. Cell Physiol. 234 (2019) 6254–6262, https://doi.org/10.1002/jcp.27356.
[58] B. Li, Z. Guo, Q. Liang, H. Zhou, Y. Luo, S. He, Z. Lin, lncRNA DGCR5 Up-regulates TGF-β1, increases cancer cell stemness and predicts survival of prostate cancer patients, Cancer Manag Res. 11 (2019) 10657–10663, https://doi.org/10.2147/CMAR.S231112.
[59] C. Stewart, C. Ralyea, S. Lockwood, Ovarian cancer: an integrated review, Semin Oncol. Nurs. 35 (2019) 151–156, https://doi.org/10.1016/j.soncn.2019.02.001.
[60] U. Menon, C. Karpinskyj, A. Gentry-Maharaj, Ovarian cancer prevention and screening, Obstet. Gynecol. 131 (2018) 909–927, https://doi.org/10.1097/AOG.0000000000002580.
[61] H. Chen, X. Tian, Y. Luan, H. Lu, Downregulated long noncoding RNA DGCR5 acts as a new promising biomarker for the diagnosis and prognosis of ovarian cancer, Technol. Cancer Res. Treat. 18 (2019), 1533033819896809, https://doi.org/10.1177/1533033819896809.
[62] J. Lei, B. Andrae, A. Ploner, C. Lagheden, C. Eklund, Nordqvist Kleppe, J. Wang, F. Fang, J. Dillner, K.M. Elfström, P. Sparén, Cervical screening and risk of adenosquamous and rare histological types of invasive cervical carcinoma: population based nested case-control study, BMJ 365 (2019) 1207, https://doi.org/10.1136/bmj.l1207.
[63] C. Xu, Y. Yu, X. Li, H. Sun, Value of integrated PET-IVIM MRI in predicting lymphovascular space invasion in cervical cancer without lymphatic metastasis, Eur. J. Nucl. Med. Mol. Imaging (2021), https://doi.org/10.1007/s00259-021-05208-3.
[64] Y. Liu, Y. Chang, S. Lu, Y.Y. Xiang, Downregulation of long noncoding RNA DGCR5 contributes to the proliferation, migration, and invasion of cervical cancer by activating Wnt signaling pathway, J. Cell Physiol. 234 (2019) 11662–11669, https://doi.org/10.1002/jcp.27825.
[65] L.Y. Yuan, X. Qin, L. Li, J. Zhou, M. Zhou, X. Li, Y. Xu, L. Cheng, H. Xing, Overexpression of LINC00037 represses cervical cancer progression by activating mTOR signaling pathway, J. Cell Physiol. 234 (2019) 13353–13360, https://doi.org/10.1002/jcp.28012.
[66] F. Yang, Y.L. Huang, DGCR5 suppresses the EMT of pediatric primary glioblastoma multiforme cell and serves as a prognostic biomarker, Eur. Rev. Med. Pharm. Sci. 23 (2019) 10024–10034, https://doi.org/10.26355/eurrev_201911_19569.
[67] Z. He, J. Long, C. Yang, B. Gong, M. Cheng, Q. Wang, J. Tang, LncRNA DGCR5 plays a tumor-suppressive role in glioma via the miR-21/Smad7 and miR-23a/PTEN axes, Aging 12 (2020) 20285–20307, https://doi.org/10.18632/aging.103800.
[68] X. Wu, P. Hou, Y. Qiu, Q. Wang, X. Lu, Large-scale analysis reveals the specific clinical and immune features of DGCR5 in glioma, Onco Targets Ther. 13 (2020) 7531–7543, https://doi.org/10.2147/OTT.S257050.
[69] D. Jiang, C. Wang, J. He, Long non-coding RNA DGCR5 incudes tumorigenesis of triple-negative breast cancer by affecting Wnt/β-catenin signaling pathway, J. BUON 25 (2020) 702–708.
[70] F. Chen, S. Yin, J. Zhu, P. Liu, C. Yang, Z. Feng, Z. Deng, lncRNA DGCR5 acts as a tumor suppressor in papillary thyroid carcinoma via sequestering miR-2861, Exp. Ther. Med. 17 (2019) 895–900, https://doi.org/10.3892/etm.2018.7012.
[71] M. Huarte, The emerging role of lncRNAs in cancer, Nat. Med. 21 (2015) 1253–1261, https://doi.org/10.1038/nm.3981.
[72] D. Hessels, Klein Gunnewiek, I. van Oort, H.F. Karthaus, G.J. van Leenders, B. van Balken, L.A. Kiemeney, J.A. Witjes, J.A. Schalken, DD3(PCA3)-based molecular urine analysis for the diagnosis of prostate cancer, Eur. Urol. 44 (2003) 8–15, https://doi.org/10.1016/s0302-2838(03)00201-x.
[73] M.J. Bussemakers, A. van Bokhoven, G.W. Verhaegh, F.P. Smit, H.F. Karthaus, J. A. Schalken, F.M. Debruyne, N. Ru, W.B. Isaacs, DD3: a new prostate-specific gene, highly overexpressed in prostate cancer, Cancer Res. 59 (1999) 5975–5979.
[74] J.B. de Kok, G.W. Verhaegh, R.W. Roelofs, D. Hessels, L.A. Kiemeney, T.W. Aalders, D.W. Swinkels, J.A. Schalken, DD3(PCA3), a very sensitive and specific marker to detect prostate tumors, Cancer Res. 62 (2002) 2695–2698.
[75] M. Tinzl, M. Marberger, S. Horvath, C. Chypre, DD3PCA3 RNA analysis in urine—a new perspective for detecting prostate cancer, Eur. Urol. 46 (2004) 182–186, https://doi.org/10.1016/j.eururo.2004.06.004.
[76] J. Groskopf, S.M. Aubin, I.L. Deras, A. Blase, S. Bodrug, C. Clark, S. Brentano, J. Mathis, J. Pham, T. Meyer, M. Cass, P. Hodge, M.L. Macairan, L.S. Marks, H. Rittenhouse, APTIMA PCA3 molecular urine test: development of a method to

aid in the diagnosis of prostate cancer, Clin. Chem. 52 (2006) 1089–1095, https://doi.org/10.1373/clinchem.2005.063289.

[77] R. Huang, X. Wang, W. Zhang, G. Zhangyuan, K. Jin, W. Yu, Y. Xie, X. Xu, H. Wang, B. Sun, Down-regulation of LncRNA DGCR5 correlates with poor prognosis in hepatocellular carcinoma, Cell Physiol. Biochem. 40 (2016) 707–715, https://doi.org/10.1159/000452582.

[78] Z. Jing, S. Guo, P. Zhang, Z. Liang, LncRNA-associated ceRNA network reveals novel potential biomarkers of laryngeal squamous cell carcinoma, Technol. Cancer Res. Treat. 19 (2020), 1533033820985787, https://doi.org/10.1177/1533033820985787.