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Review Article

Progress and assessment of lncRNA DGCR5 in malignant phenotype and immune infiltration of human cancers

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Abstract: As a special type of noncoding RNA, long noncoding RNAs (lncRNAs) have vital roles during the development of human cancers and may be novel predictors or therapeutic targets for improving the management of patients with cancer. DiGeorge syndrome critical region gene 5 (*DGCR5*) is a prominent tumor-associated lncRNA, exerting tumor suppressor or oncogenic roles in various cancers. Previous studies have reported that *DGCR5* has low expression in most types of cancers but high expression in triple-negative breast cancer, gallbladder cancer, and lung cancer. And *DGCR5* expression is related to many hallmarks of cancer types, including cell proliferation, invasion, migration, apoptosis, stemness, and therapeutic responsiveness. Additionally, the pivotal molecules involved in DGCR5 regulation of signaling pathways are attributed to cancer hallmarks related to the pathogenesis of different types of malignant tumors. Herein, we discuss the DGCR5 expression pattern in various types of tumor tissues and relationships between DGCR5 expression and immune cell infiltration and immune purity. We also review our current understanding of DGCR5 in carcinogenesis and its potential application as a prognostic biomarker or therapeutic target in human cancers.

Keywords: DGCR5, long noncoding RNA, human cancers, function, molecular mechanisms, TCGA

Introduction

Despite the recent scientific and technological advancements of diagnostics and therapeutics, cancer is still one of the most serious life-threatening diseases worldwide [1, 2]. There are numerous factors that contribute to the development of cancers, such as genetic mutations [3-5], aberrant expression of protein-coding genes [6], and dysregulation of noncoding RNAs [7]. Interestingly, less than 2% of the human genome is ultimately translated into proteins while more than 90% of the genome is transcribed into noncoding RNAs [8]. Although these RNAs are not translated into proteins, they still play important roles in various cellular and physiological functions [9]. Long noncoding RNAs (lncRNAs) are an emerging class of noncoding RNAs that are longer than 200 nucleotides and considered to be vital regulators of gene expression and the carcinogenesis process [10]. Notably, lncRNA is expected to modulate gene expression at the post-transcriptional and transcriptional levels and then regulate the malignant cell phenotype, including apoptosis, proliferation, migration, and invasion [11]. With the completion of the Encyclopedia of DNA Elements project, it is estimated that the human genome encodes more than 28,000 lncRNAs, most of which have yet to be researched [12]. However, it is difficult to characterize the functions of so many lncRNAs in a variety of cancers [13].

DiGeorge syndrome critical region gene 5 (*DGCR5*), also known as lncRNA0037, was first discovered in Huntington's disease [14]. Studies have since reported the expression pattern and function of *DGCR5* in various malignancies, including lung [15, 16], liver [17, 18], breast [19], bladder [20], gallbladder [21], and colorectal cancers [22]. Interestingly, *DGCR5* was

found to be downregulated in most tumor tissues, and this decrease enhanced cell proliferation, migration, and invasion via activation of the Wnt signaling pathway in cervical cancer [23]. Some researchers found that this lncRNA has low expression in hepatocellular carcinoma and that abnormal *DGCR5* expression is related to poor prognosis. However, *DGCR5* was upregulated in gallbladder cancer tissue and cell lines and the silencing of this lncRNA impaired cell proliferation and migration by the JUK and p38 MAPK pathways [21]. These results suggest that this lncRNA has different roles in the pathogenesis of different cancers.

Here, we focus on the available evidence regarding the aberrant expression, function, and molecular mechanism of *DGCR5*. In addition, we assessed the differential expression of *DGCR5* in 23 tumor tissues compared with corresponding normal tissues based on The Cancer Genome Atlas (TCGA, https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga). In our study, we also explored gene expression of DGCR5 among various cancers and assessed the correlation between *DGCR5* expression and overall survival time. Furthermore, we discussed the potential clinical value of *DGCR5* as a potential prognosis predictor and promising therapeutic target.

Aberrant expression and biological function of lncRNA DGCR5 in cancers

In several human cancers, alterations in *DGCR5* expression or function regulate subsequent malignant development including cell proliferation, migration, invasion, apoptosis, cell cycle arrest, and stemness characteristics. The expression pattern and biological function of *DGCR5* are depicted in **Table 1**.

Lung cancer

Lung cancer is one of the most common cancers worldwide, with 5-year overall survival rates vary from 4-17% [24, 25]. Approximately 80% of all lung cancers are non-small cell lung cancer (NSCLC) [26], 50% of which are lung adenocarcinoma (LUAD) [27]. The major features of NSCLC include tumor growth, invasion, and metastasis [28, 29]. Thus, it is essential to fully understand the pathogenesis of lung cancer and identify novel therapeutic targets for NSCLC.

A growing body of evidence has indicated that the aberrant expression of lncRNA *DGCR5* may be related to the initiation and progression of NSCLC. Liu et al. found that *DGCR5* had high alteration frequencies in 624 lncRNAs according to sample analysis from the TCGA database, and *DGCR5* was correlated with better overall survival in lung cancer [30]. Wang et al. reported *DGCR5* is upregulated in LUAD tissue specimens and cell lines ($P<0.05$). Silencing *DGCR5* not only reduced proliferation of LUAD cells and induced LUAD cell apoptosis in vitro but also was closely related to smaller tumor size [16]. In previous research by Wang et al., increased *DGCR5* was found in the enriched cancer stem cells (CSCs) of NSCLC and *DGCR5* knockdown suppressed the stemness of NSLCL [15]. Another report revealed that *DGCR5* is significantly upregulated in NSCLC tissues compared with adjacent counterparts but, in its oncogenic role, suppressed NSCLC cell migration and invasion [31]. However, some research groups showed that *DGCR5* is markedly lower in tissue specimens than adjacent counterparts from patients with lung cancer [32-34] and correlated with poor prognosis [32]. Functionally, overexpressed *DGCR5* inhibited NSCLC cell growth, migration, and invasion [32].

Taken together, these results reveal conflicting evidence regarding the expression and role of *DGCR5* in lung cancer. In clinical samples, this observation may be explained by the heterogeneity of cancerous cells and environmental factors.

Gallbladder cancer

Gallbladder cancer (GBC) is a highly aggressive malignancy with extremely poor prognosis [35, 36]. *DGCR5* was identified as one of the lncRNAs that participates in GBC tumorigenesis and progression. Exploring the expression and functions of *DGCR5* in GBC, Liu et al. found that *DGCR5* is higher in GBC neoplastic tissues and cell lines [21]. Importantly, silencing *DGCR5* inhibited cell proliferation, invasion, and migration while significantly enhancing apoptosis and cell cycle arrest. Moreover, xenograft growth assays showed that *DGCR5* knockdown reduces tumor volume and weight [21].

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) ranks as the third leading cause of cancer-related death

Table 1. The expression pattern and biological function of DGCR5 in a variety of cancers

Cancer types	Expression	Role	Overexpression of GDCR5 related with clinicopathological parameters	Overexpression of GDCR5 associated with prognosis	Ref
Lung cancer	high	enhance CSC-like traits			[15]
	low	anti-apoptosis	large tumor size	poor	[16]
	low	restrain cell growth, migration, invasion	small tumor size, less lymph metastasis, less distant metastasis	favorable	[33]
	low	restrain proliferation, migration and invasion	less lymphatic metastasis	favorable	[32]
	high	enhance migration and invasion			[31]
Gallbladder cancer	high	enhance proliferation, migration, invasion, and induced apoptosis, cell cycle arrest			[21]
Hepatocellular carcinoma	low	restrain cell growth, migration, and invasion			[17]
	low	restrain cell growth, migration and invasion			[18]
	low	less vascular invasion		favorable	[43]
Cervical cancer	low	pro-apoptosis, restrain proliferation, migration, and invasion			[23]
	low	pro-apoptosis, and restrain the cell proliferation, migration and invasion			[44]
Laryngeal cancer		radioresistance			[48]
		enhance CSC-like properties			[47]
Ovarian Cancer	low		small tumor size, less lymph metastasis, less distant metastasis	favorable	[45]
Triple-negative breast cancer	high	enhance proliferation, migration and invasion			[19]
Gastric cancer	low	suppress proliferation, invasion and migration, and pro-apoptosis	less Lymphatic metastasis, early TNM stage	favorable	[46]
Bladder cancer	low	restrain proliferation, invasion, EMT, and pro-apoptosis		favorable	[20]
Colorectal cancer	low	restrain proliferation	early clinical stage		[22]
Glioma	low		early WHO grade	favorable	[49]
Pancreatic cancer	low	pro-apoptosis			[50]
Thyroid carcinoma	low	restrain proliferation and invasion			[51]
Prostate Cancer	low			favorable	[52]

worldwide [37]. Emerging evidence has demonstrated the critical roles of lncRNA in the development of HCC [38-41]. As a newly identified lncRNA, *DGCR5* has attracted the attention of many researchers. Wang et al. revealed that *DGCR5* has lower expression in HCC tissue and cells than in normal liver tissue and cell lines. Functionally, increased *DGCR5* inhibited cell growth, migration, and invasion in vitro [17]. Consistent with these findings, overexpression of *DGCR5* restrained tumor growth in vivo. Similarly, a few studies have shown that *DGCR5* is relatively downregulated in HCC tissues specimens and cell lines compared with adjacent counterparts and normal liver cell lines [18, 42, 43]. Low expression of *DGCR5* was closely associated with worse prognosis (P=0.0019), and *DGCR5* expression was revealed as an independent prognostic factor in HCC by receiver operating characteristic curve analysis [43]. These results indicate that this lncRNA is a potential biomarker of cancer development.

Cervical cancer

The expression of *DGCR5* was relatively decreased in human cervical cancer cells compared with primary normal cervical squamous cells [23, 44]. Upregulation of *DGCR5* restrained cervical cancer cell proliferation, invasion, and migration but induced cell apoptosis. Conversely, downregulation of *DGCR5* exhibited an opposite process in vitro [44]. Moreover, in animal models established by SiHa cells, *DGCR5* was found to suppress tumor progression [44].

Ovarian cancer

The *DGCR5* level was dramatically decreased in 66 pairs of ovarian cancer tissues compared with normal tissues [45]. Specifically, the level of *DGCR5* was reduced by 65.79% in neoplastic tissues compared with nonneoplastic tissues in the Gene Expression Omnibus datasets (GSE119056). In addition, low expression of *DGCR5* was significantly associated with advanced clinical stage, large tumor size, present distant metastasis, positive lymph node metastasis, and poor prognosis in patients with ovarian cancer. Univariate cox regression analysis and receiver operating characteristic curve analysis revealed that low *DGCR5* expression is an independent risk factor. All of these results suggest that lncRNA *DGCR5* is a potential predictor for progression and prognosis in patients with ovarian cancer [45].

Gastric cancer

DGCR5 plays a significant regulatory role in a variety of malignancies, including gastric cancer. The transcription level of *DGCR5* was remarkably low in 98 gastric cancer tissue specimens from patients with gastric cancer, similar to the results identified in gastric cancer cell lines [46]. Correlation analysis showed that downregulated *DGCR5* is related to advanced TNM stage and more lymphatic metastasis. Moreover, overexpression of *DGCR5* inhibited cell proliferation, invasion, and migration. These results support *DGCR5* as a tumor-suppressive lncRNA in gastric cancer [46].

Other cancers

In human laryngeal cancer, Tang et al. reported that *DGCR5* contributes to the radioresistance and cancer stem cell-like phenotypes of laryngeal carcinoma cells in vitro [47, 48]. Other studies have shown that *DGCR5* has low expression in tumor tissue and functions as a suppressor of tumor progression in bladder cancer [20], colorectal cancer [22], glioma [49], pancreatic cancer [50], papillary thyroid carcinoma [51], and prostate cancer [52].

Subcellular location, expression, and overall survival information of DGCR5

DGCR5 is affiliated with the lncRNA class. The genomic location for the *DGCR5* gene is chr22: 18,969,860-19,031,242. The cytogenetic band is located in chromosome 22q11.21 as shown in **Figure 1A**. To further explore the differential expression of *DGCR5* in normal human tissues, we utilized the GeneCard online database (https://www.genecards.org) and found that this gene is highly expressed in the brain cerebellar hemisphere, cerebellum, cortex, frontal cortex, and anterior cingulate cortex as shown in **Figure 1B**.

Gene Expression Profiling Interactive Analysis (GEPIA) [53] online data analysis (http://gepia.cancer-pku.cn/) was applied to explore the DGCR5 expression among 23 types of tumor tissues and their adjacent nontumor tissues. In this study, we validated that DGCR5 expression is significantly overexpressed in three types of tumors-kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, and LUAD compared with adjacent normal tissues (**Figure 2A-C**). In addition, we further analyzed the relationship between DGCR5 expression and

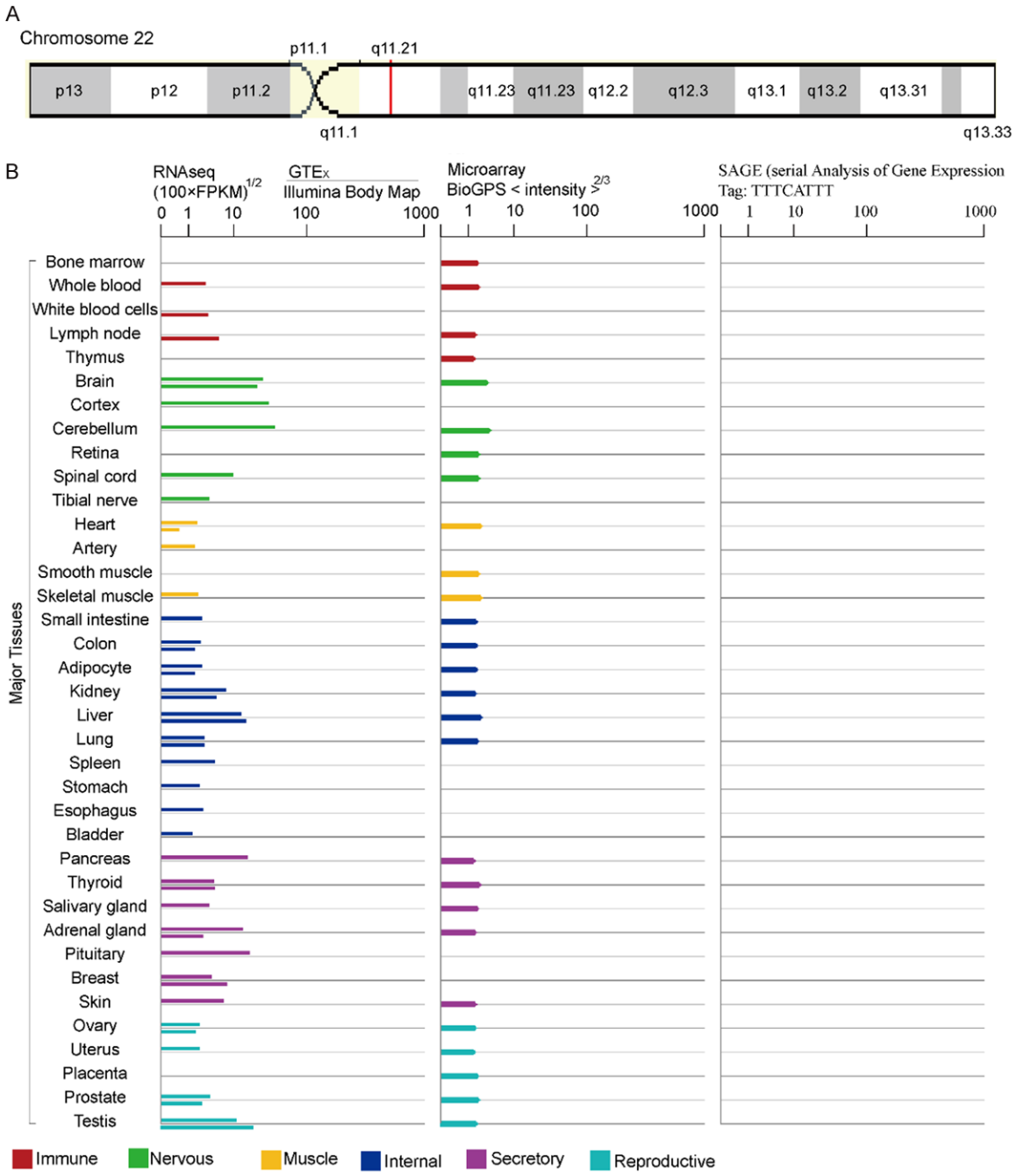

Figure 1. The genomic location and expression of *DGCR5*. A. The chromosome location of *DGCR5* in 22q11.21, chr22: 18,969,860-19,031,242. B. The expression of *DGCR5* in normal human tissues.

patient prognosis. The results of this analysis indicated that increased DGCR5 in four tumors (cholangiocarcinoma, colon adenocarcinoma, kidney chromophobe, and uterine corpus endometrial carcinoma) showed poor prognosis (**Figure 2D-F**). However, in low grade glioma (LGG), the decreased *DGCR5* mRNA expression indicated favorable prognosis (**Figure 2H**).

DGCR5 related immune cells infiltrations landscape

The tumor immune microenvironment plays potential roles in tumor immunology, which might associate with carcinogenesis and tumor prognosis. LncRNAs play important roles in the regulating immune response and the tumor

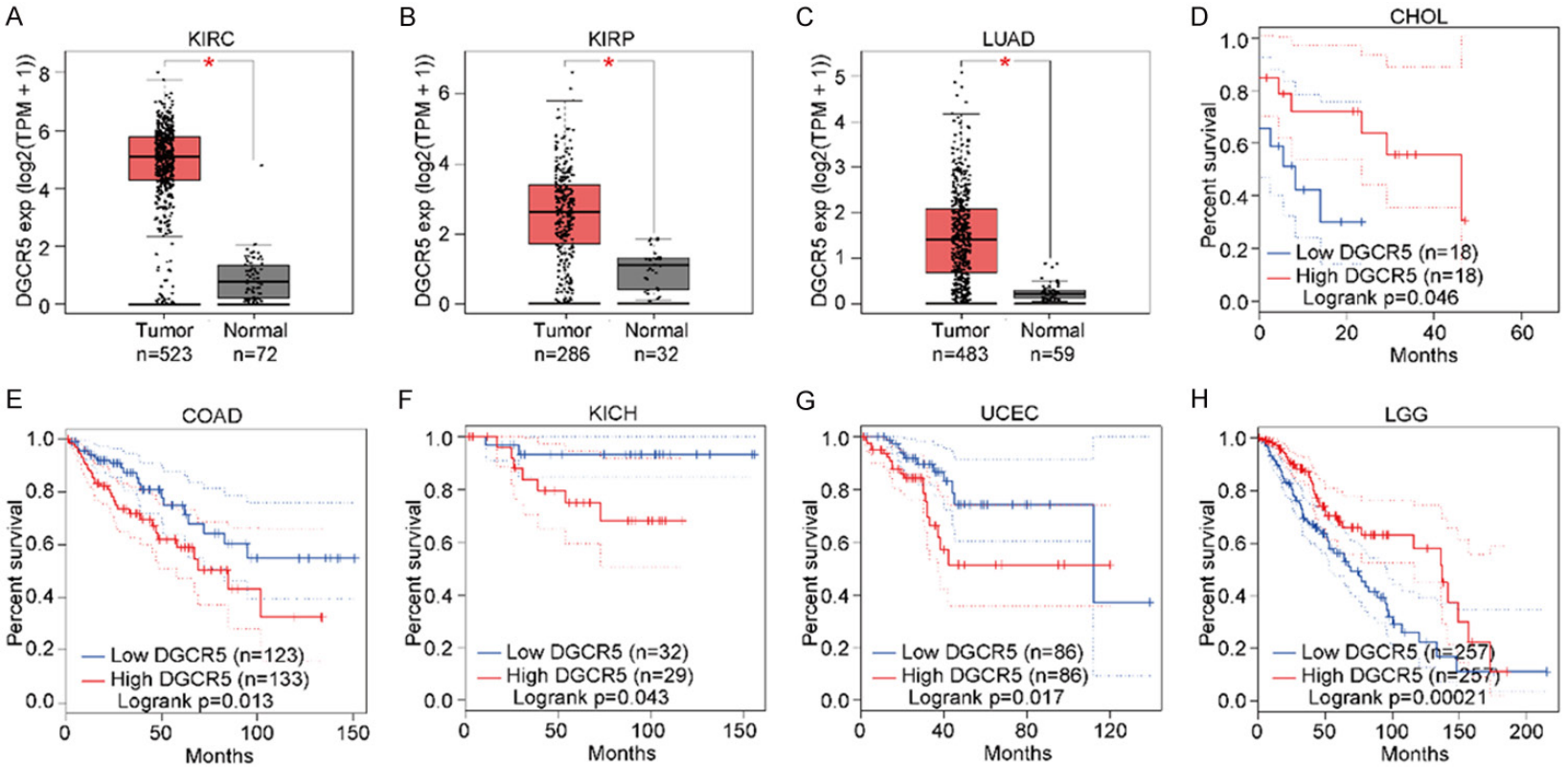

Figure 2. The mRNA expression and overall survival rate of *DGCR5* in pan-cancers. A. *DGCR5* expression was significantly upregulated in kidney renal clear cell carcinoma (KIRC) (P<0.05). B. *DGCR5* expression was significantly upregulated in kidney renal papillary cell carcinoma (KIRP) (P<0.05). C. *DGCR5* expression was significantly upregulated in lung adenocarcinoma (LUAD) (P<0.05). D. Overexpressed *DGCR5* in the cholangiocarcinoma (CHOL) cohort showed longer overall survival time (P=0.046). E. Overexpressed *DGCR5* in colon adenocarcinoma (COAD) showed worse prognosis (P=0.013). F. Overexpressed *DGCR5* in kidney chromophobe (KICH) had shorter overall survival time (P=0.043). G. Downregulated *DGCR5* in uterine corpus endometrial carcinoma showed significantly better prognosis (P=0.017). H. Downregulated *DGCR5* in LGG showed significantly worse prognosis (P=0.00021).

immune microenvironment [54]. *DGCR5* is a novel identified lncRNA, which is involved in immune-related biological processes, shows significant correlation with immune cells infiltration and immune checkpoints in glioma [49]. Therefore, further detection the relationship between immune cells infiltration landscape and *DGCR5* of patient tumors may guide immunotherapy treatment intervention target. We comprehensively described the *DGCR5* expression from immune cell infiltration and immune purity based on the Tumor IMmune Estimation Resource database (https://cistrome.shinyapps.io/timer/) [55, 56]. Analysis using this database indicated that *DGCR5* expression has close relationships with immune cell infiltration and immune purity. For example, in LGG, immune cell infiltration showed a significantly negative correlation with *DGCR5* expression. However, in breast cancer, colon adenocarcinoma, bladder carcinoma, and rectum adenocarcinoma, the immune cells were positively correlated with *DGCR5* expression. From this study's results, we could elucidate the relationship between immune cells infiltration and immune purity among pan-cancers. Therefore, these results demonstrated that *DCGR5* may be involved in multiple immune cell regulations and have potential prognostic value in cancer immune therapies (**Figure 3A**). In **Figure 3B**, we concluded that lncRNA DGCR5 was negatively correlated with CD4+ T cell (r=-0.493, P= 1.53e-30), macrophage (r=-0.49, P=6.62e-30), and dendritic cell (r=-0.405, P=3.11e-20) infiltration in LGG. These results indicate that DGCR5 has close relationship with immune cells infiltration, and DGCR5 might be a novel immune target in cancer therapies.

Molecular mechanisms related to DGCR5

LncRNAs function through complex molecular mechanisms, such as interacting with RNA, DNA, and proteins. **Table 2** summarizes the current data regarding DGCR5 target genes and downstream signaling pathways.

One important mechanism of lncRNA is that it can act as competing endogenous RNA (ceRNA) [57-59]. This means that lncRNA can sponge miRNA from target mRNA, thereby constructing a triple network of lncRNA-miRNA-mRNA [60]. This molecular mechanism has been shown to widely participate in the regulation of malignant features of the tumor cell [61]. *DGCR5* has been identified as a ceRNA. For instance, in lung cancer, it is reported that *DGCR5* could sponge some miRNAs from downstream target mRNA to directly regulate gene expression [15, 16, 31-34] (**Figure 4**). In pancreatic cancer, *DGCR5* functions as a tumor inhibitor by increasing the expression of Bcl-2/adenovirus E1B-19kDa-interacting protein 3, which activates the p38 MAPK signaling pathway by outcompeting miR-27a-3p [50].

Similar modalities exist in a variety of tumors. For example, Tang et al. reported that *DGCR5* induces CSC-like properties through sponging miR-506 via activation of the Wnt pathway in laryngeal carcinoma cells [47]. Wang et al. found that *DGCR5* was able to restrain the progression of HCC by sponging miR-346 [18]. In gastric cancer, *DGCR5* acted as a tumor-suppressive lncRNA by regulating PTEN and BTG1 expression via binding to miR-23b [46].

DGCR5 not only acts as ceRNA to regulate protein level in the cytoplasm but also influences chromatin remodeling protein. In bladder cancer, *DGCR5* interacts with AT-rich interaction domain 1A (ARID1A), a chromatin remodeling protein recruited by *DGCR5* and enriched on the promoter of P21. This interaction leads to increased expression of P21 and a reduction in cyclin D1 expression. The aberrant expression of P21 and ARID1A inhibits cell cycle progression, leading to impaired cell proliferation and enhanced apoptosis [20]. Furthermore, the overexpression of DGCR5 restricted cell invasion and migration by inhibiting the epithelial-mesenchymal transition (EMT) via downregulation of N-cadherin and upregulation of E-cadherin. Thus, DGCR5 transcriptionally promotes P21 expression to inhibit tumor progression [20] (**Figure 5**).

Conclusions

Increasing evidence has revealed that lncRNAs participate in the initiation, progression, and treatment responsiveness of cancer by acting as tumor suppressors or oncogenes [62-64]. Various lncRNAs were found to be aberrantly upregulated or downregulated in cancers and were closely associated with clinicopathological parameters and patient prognosis. Further clarification of the underlying mechanism of lncRNAs may contribute to the development of

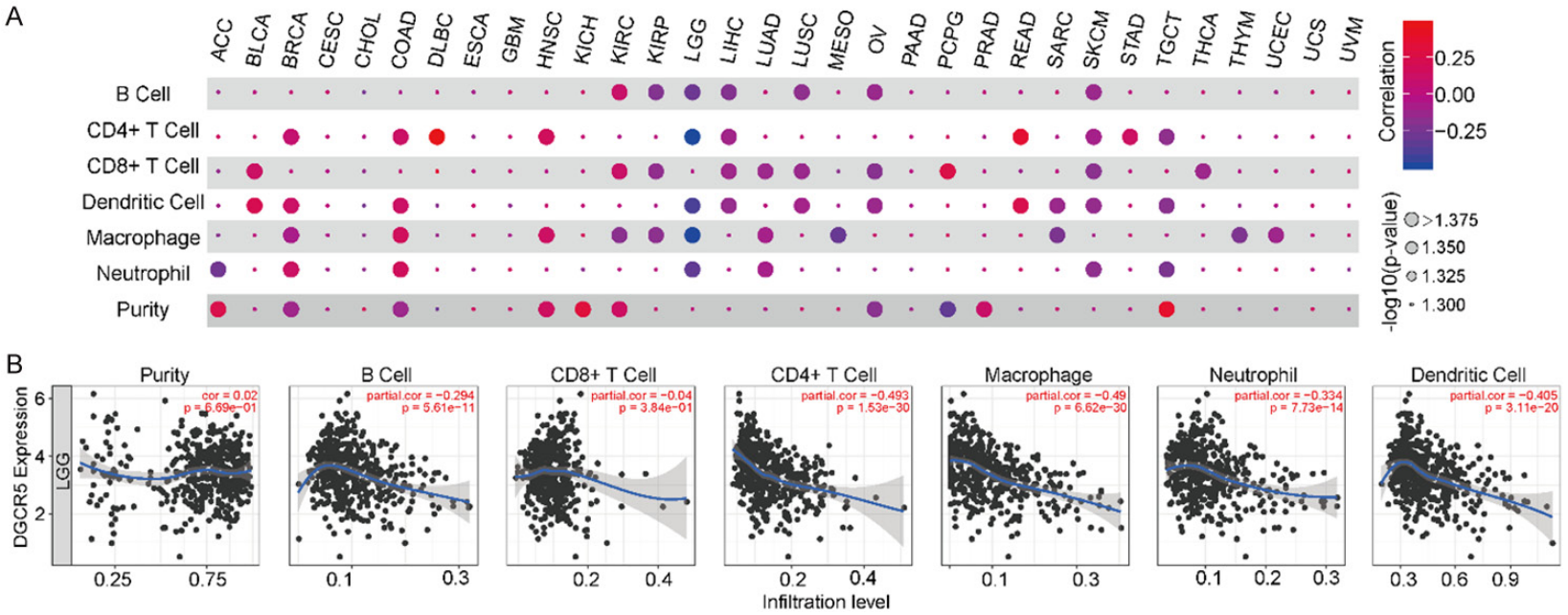

Figure 3. Immune cell infiltration and immune purity landscape with DGCR5 expression. A. The correlation ship between immune cells infiltration and lncRNA DGCR5 expression among pan-cancers. B. The detail immune purity and immune cells infiltration status of LGG.

Table 2. The target genes of DGCR5 and downstream signaling pathways

Cancer types	Target genes	Related signaling pathway	Ref
Lung cancer	miR-330-5p/CD44		[15]
	hsa-miR-22-3p		[16]
	miR-873-5p/TUSC3		[33]
	miR-1180		[32]
	miR-218-5p		[31]
	miR-211-5p/EPHB6		[34]
Gallbladder cancer	miR-3619-5p	MEK/ERK1/2 and JNK/p38 MAPK	[21]
Hepatocellular carcinoma		Wnt/β-catenin	[17]
	miR-346/KLF14		[18]
Cervical cancer		Wnt	[23]
		mTOR	[44]
Laryngeal cancer	miR-195		[48]
	miR-506	Wnt	[47]
Ovarian Cancer			[45]
Triple-negative breast cancer		Wnt/β	[19]
Gastric cancer	miR-23b	PTEN and BTG1	[46]
Bladder cancer	ARID1A	P21	[20]
Colorectal cancer	miR-21		[22]
Glioma			[49]
Pancreatic cancer	miR-27a-3p/BNIP3	p38 MAPK	[50]
Thyroid carcinoma	miR-2861		[51]
Prostate Cancer		TGF-β1	[52]

new diagnosis and treatment strategies for cancer.

DGCR5 is a novel lncRNA that has been identified to play an antioncogene or oncogene role in different types of cancer. The majority of current data indicates that *DGCR5* is downregulated in multiple malignancies including lung cancer, hepatocellular carcinoma, cervical cancer, laryngeal cancer, ovarian cancer, bladder cancer, colorectal cancer, glioma, pancreatic cancer, thyroid carcinoma, and prostate cancer. In these cancer types, downregulated *DGCR5* is correlated with large tumor size, advanced clinical stage, more metastasis, and short overall survival time. Thus, *DGCR5* might serve as potent prognostic biomarker. Conversely, *DGCR5* is highly expressed in triple-negative breast cancer, gallbladder cancer, and lung cancer, where it plays a protumor role. In these three cancer types, knockdown of *DGCR5* could inhibit tumor cell proliferation, invasion, and migration; facilitate apoptosis; and contribute to a favorable prognosis. Furthermore, lncRNAs were involved in complicated immune regulation [65, 66]. The resent data showed that DGCR5 was significantly correlation with stromal and immune cell populations, and immune response.

We also noticed that the expression and function of *DGCR5* are different in diverse cancers, even in the same type of cancer such as in lung cancer. These differences may be driven by tumor tissue heterogeneity, which is a key hallmark of cancer [67], mainly caused by genetic mutation. Increasing genetic mutations can alter genotype and phenotype within the tumor cell, thereby contributing to genomic instability in cancer cells. Further study of this issue may help to better understand the underlying mechanism of cancer and help provide more precise treatment. Furthermore, most studies on *DGCR5* have been focused on the regulation of its transcription levels while in-depth mechanistic research has been limited. As a result, the specific mechanism of *DGCR5* has not been fully explored. Therefore, *DGCR5*, as a promising lncRNA, requires increasingly comprehensive and in-depth study prior to its use for clinical applications.

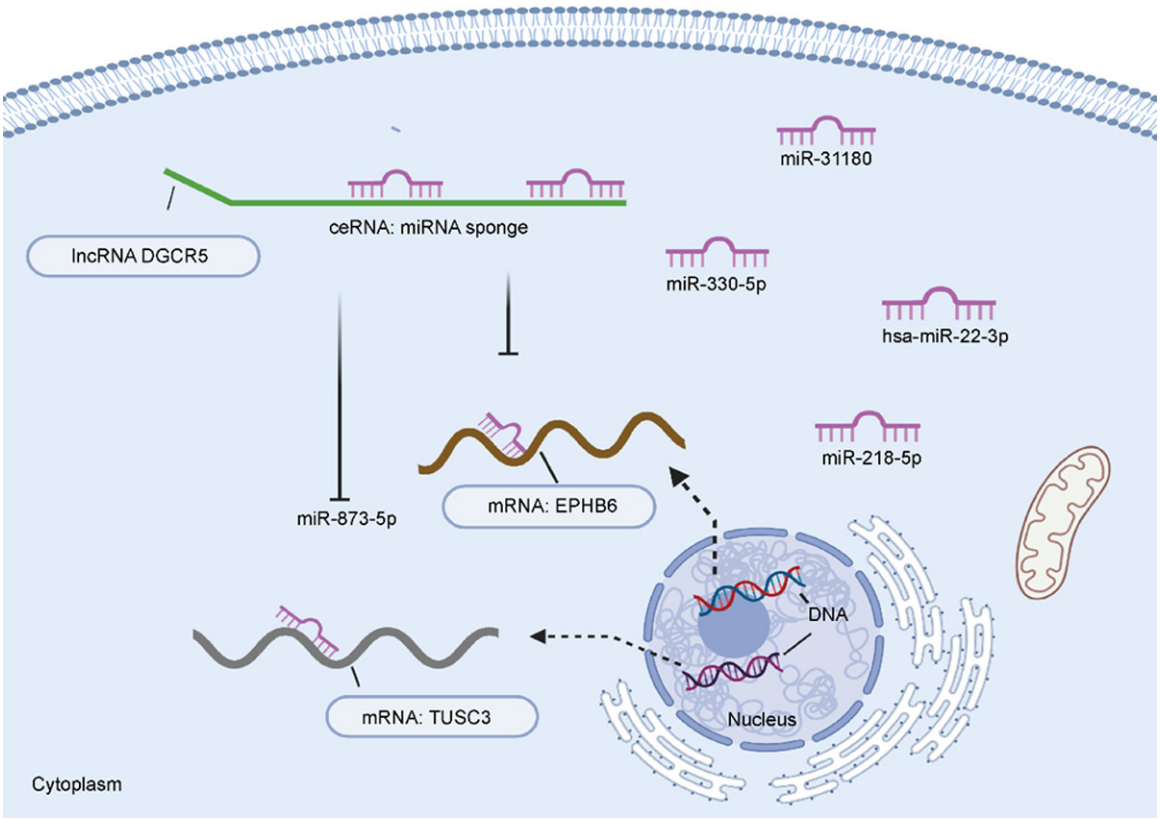

Figure 4. The cellular regulatory landscape of lncRNA DGCR5 in various cancers. LncRNA DGCR5 act as a ceRNA and miRNA sponge and binds to miRNAs to inhibit lung cancer progression. It acts by negatively targeting miRNA and then mediating its downstream target genes, such as the *DGCR5*/miR-873-5P/TUSC3 axis or the DGAR5/miR211-5p/EPHB6 axis.

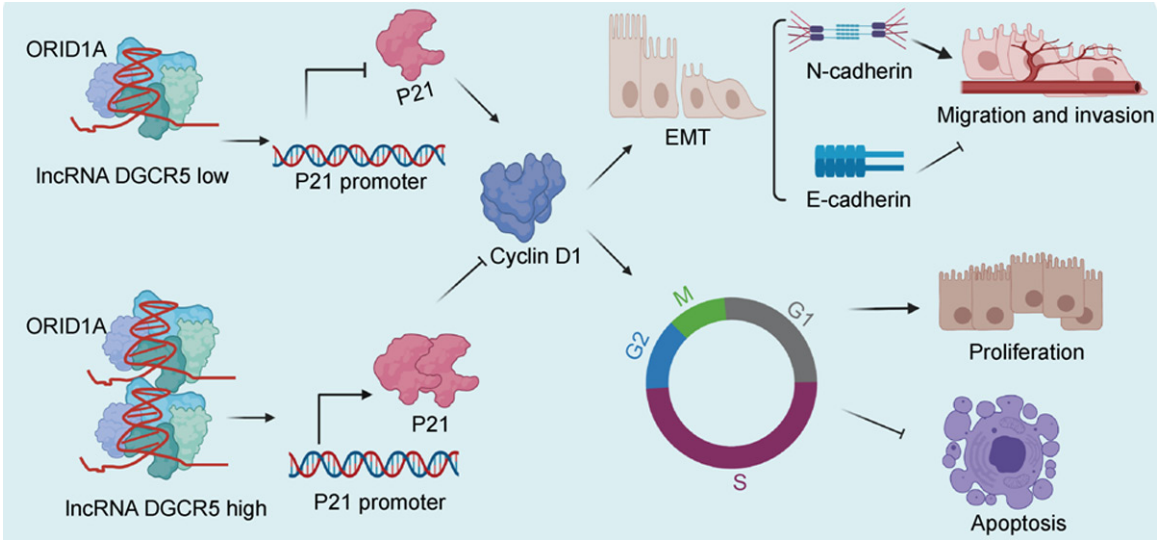

Figure 5. LncRNA *DGCR5* regulates bladder cancer cell proliferation, invasion, migration, and apoptosis by affecting P21 expression. Upregulated DGCR5 interacts the chromatin remodeling proteins ORID1A to promote P21 transcription. Then P21 becomes elevated and cyclin D1 decreases, thus inhibiting cell proliferation and dramatically increasing apoptosis by regulating the cell cycle. In addition, upregulated DGCR5 inhibits migration and invasion by EMT via downregulation of N-cadherin and upregulation of E-cadherin. Meanwhile, the downregulation of DGCR5 exhibits the opposite process.

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Disclosure of conflict of interest

None.

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