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ORIGINAL ARTICLE

Long Noncoding RNAs in Colorectal Adenocarcinoma; an *in silico* Analysis

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Abstract

Long noncoding RNAs (lncRNAs) are lengthy noncoding transcripts which are involved in critical signaling pathways including cell cycle and apoptosis so it is not surprising to see their altered expression in human tumors. Colorectal adenocarcinoma is one the most frequent malignancies worldwide. The role of lncRNAs in colorectal adenocarcinoma is not well understood. To study the significance of lncRNAs in colorectal adenocarcinoma, we retrieved 189 approved lncRNAs from HGNC. The genes were imported into the cBioPortal database for transcriptomic analyses. We queried all the samples from TCGA provisional colorectal adenocarcinoma with RNA-seq v2 data in our study and considered RNA dysregulation with Z-score: ±2. The lncRNA which was altered in most of the patients were considered as "significant lncRNA" for further analyses. We considered the association of candidate lncRNAs with clinicopathologic parameters of samples including tumor disease anatomic site, neoplasm histologic types, tumor stage and survival. We also compute the specificity of the significant lncRNAs expression in colorectal adenocarcinoma comparing with other human cancers in cancer portal. Our analysis showed that lncRNAs *SNHG6*, *PVT1* and *ZFAS1* allocated the maximum alteration among the colorectal cases. The expression of *SNHG6* and *ZFAS1* was more in rectal adenocarcinoma than the colon carcinoma while the *PVT1* showed the same expression levels in both tissues. However, we found that upregulation of *PVT1* has been reduced the overall survival in patients. Altogether these data showed *SNHG6*, *PVT1* and *ZFAS1*, are promising candidates for experimental research on colorectal adenocarcinoma to discover novel biomarker for this prevalent cancer.

Keywords Cancer · Biomarker · Long noncoding RNAs · *SNHG6* · *PVT1* · *ZFAS1*

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Introduction

Colorectal cancer is one of the most common causes of cancer mortality worldwide [1]. Alcohol consumption, smoking as well as obesity are the approved risk factors of colorectal cancers [2]. In addition, scientists also believe that accumulation of genetic errors plays an important role to transform the normal cells toward colorectal adenocarcinoma. Noncoding sequences of the genome seem to act as crucial modulators of cellular pathways and metabolism [3–5]. These sequences are divided to micro RNAs (miRNAs) and long noncoding RNAs (lncRNAs) [4, 6]. Although miRNAs are widely studied in tumor initiation, progression and invasion [7], the significance of lncRNAs in tumor pathogenesis are less understood [4, 7]. In fact, lncRNAs are 3'polyadenylated and 5'capped transcripts which are usually transcribed by RNA polymerase II [3, 4]. Regulation of chromatin structure, transcription, cell cycle and apoptosis are some of the functions which are attributed to these lengthy transcript [8]. Aberrant

expression of lncRNAs has been reported in several human cancers, the finding that put lncRNAs as the novel generation of cancer biomarker. Besides, cell- and tissue-specific expressions of lncRNAs as well as their stability in serum or urine make them as promising candidate markers in clinics [3, 9]. Owing to limited documents to associate the lncRNAs with colorectal adenocarcinoma, the present study was aimed to perform in silico analysis of the issue. Variety of cancer genetics and transcriptomics databases were screened to reveal the potential of lncRNAs as diagnostic markers for colorectal adenocarcinoma. The results of such projects open a new window to perform further experimental genetic analysis to the researchers who are interested in diagnostic and therapeutic approach of colorectal adenocarcinoma. In the current study, we found that lncRNA *PVT1* has significant potential to be considered as colorectal adenocarcinoma biomarker.

Materials and Methods

Choosing of lncRNAs with the Highest Gene Expression Alteration Score among Colorectal Adenocarcinoma Patients

To reveal the contribution of lncRNA in colorectal adenocarcinoma, 189 approved lncRNAs were recruited from HGNC (www.genenames.org). All the genes are inputted into the cBioPortal database (http://www.cbioportal.org) [10, 11] for transcriptomic analyses. We queried 382 samples from TCGA colorectal adenocarcinoma (TCGA, provisional) with RNA-seq v2 data in this study and considered mRNA expression Z-score threshold: ±2. The lncRNAs which were altered in more than 10% of the patients were considered as "candidate lncRNAs" for further analyses. These lncRNAs included *PVT1,* ZFAS1, and *SNHG6* due to high levels of alteration in both genomic and transcriptomic levels. Additionally, TCGA RNA-Seq raw data was extracted in R using the cgdsr (cran.rproject.org/web/packages/cgdsr/) and cbaf [12] extension packages with a threshold of ±2. The data was then presented as Heatmap plot.

Study of the Expression Level of Candidate lncRNAs in Normal Tissue

We analyzed the expression level of the candidate lncRNAs in normal colon and intestine tissue through the RNA-seq data from 53 human tissue samples from the Genotype-Tissue Expression (GTEx) project which was publicly available at gene expression atlas dataset (https://www.ebi.ac.uk/arrayexpress) [13–16].

Clinical Significance of lncRNAs with the Clinicopathologic Parameters of Colorectal Adenocarcinoma

The contribution of different lncRNAs with clinicopathologic parameters (tumor disease anatomic site, neoplasm histological type, tumor staging, and grade) was evaluated using Student's *t*-test. The extracted clinical information of cBioPortal dataset interrogated into the MATLAB software and presented as bar plot. Additionally, to reveal if the aberrant expression of candidate lncRNAs can affect the patients' survival, overall Kaplan-Meier estimate was performed in the cBioPortal database. The Log-Rank Test *P*-Value <0.05 was considered as statistically significant.

Studying of Candidate lncRNAs Co-Occurrence

We also examine if the candidate lncRNAs are co-expressed at the same time using cBioPortal interface, mutual exclusively analyses. Among 382 patients with colorectal adenocarcinoma, 154 cases showed alterations for *SNHG6*, *PVT1,* and *ZFAS1*. We evaluated the genes which were co-expressed with significant lncRNAs using Pearson's correlation analysis among these 154 cases. Then, the genes with correlation value>0.50 were selected and imported into the MATLAB R2017a software for more analysis.

The Comparison of Candidate lncRNA*s* Expression Level in Colorectal Adenocarcinoma and Other Cancers

To examine if the lncRNA expressions follow colorectal adenocarcinoma-specific manner, we considered its gene expression alteration in all other recorded tumor samples in cBioPortal. Briefly, all cancer-associated RNA-seq data were extracted from the portal. The raw data was filtered based on the z-score > +2 and < −2. The mean of the expression levels was calculated using R and the data was presented as heatmaps.

Functional Analysis of Candidate lncRNA

We considered lncRNA PVT1 for functional analysis as this lncRNA show more association with colorectal pathogenicity. To determined how the PVT1 acts, we extract all the probable interaction of PVT1 with DNA, RNA, protein especially transcription factors. We extract this information from NPInter (http://www.bioinfo.org/NPInter/search.php) dataset which is a catalogs experimentally determined functional interaction between ncRNAs and proteins, mRNAs or genomic DNA sequences [17].

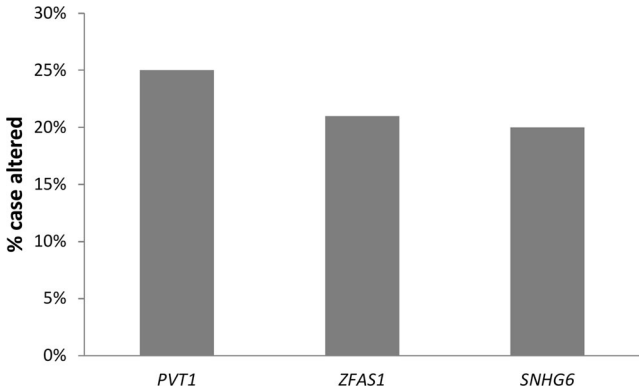

Fig. 1 Altered in 154 (41%) of 379 sequenced cases/patients (379 total)

Statistical Analysis

R statistical software and MATLAB R2017a software were used to all of the analyses including the t-test, heatmap, and correlation analysis and *P*-values less than 0.05 were considered significant.

Results

Sixty lncRNAs were Found to be Dysregulated in Colorectal Adenocarcinoma Samples

From 189 lncRNAs, 60 lncRNAs were dysregulated in colorectal adenocarcinoma samples among which *PVT1*, *ZFAS1* and *SNHG6* were altered in 25% ($n = 96$), 21% ($n = 91$) and 20% ($n = 77$) of patients. These lncRNAs were considered for more analyses (Fig. 1).

Long Noncoding RNAs *PVT1*, *ZFAS1*, and *SNHG6* are also Expressed in Normal Colon and Rectum Tissues

As shown in Fig. 2, the three candidate lncRNAs *PVT1*, *ZFAS1* and *SNHG6* are also expressed in normal tissue among which *SNHG6* and *PVT1* have been allocated the highest and lowest tissue expression level, respectively while that *ZFAS1* had low expression score.

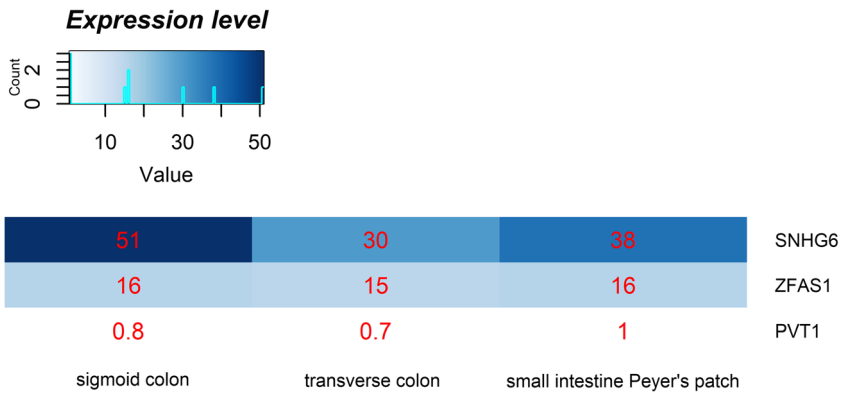

Fig. 2 Expression level analysis of lncRNAs *PVT1*, *SNHG6* and *ZFAS1* in normal colon and intestine tissues. Data was obtained from GTEx project. The red score illustrates the expression level score in RNA-seq mRNA baseline

Tumor Disease Anatomic Site is Associated with lncRNA Expression Pattern of Candidate lncRNAs

Classifying the specimens based on tumor anatomic site, demonstrated that only the lncRNA *SNHG6* has been preferentially upregulated in Rectum tumors than the colon (*P*-Value = 0.01) while the others were not statistically significant (Fig. 3).

Different Neoplasm Histological Types Showed the Different Expression Pattern for Candidate lncRNAs

Classifying the specimens based on neoplasm histological type showed that the lncRNAs *SNHG6* and *ZFAS1* has been more expressed in rectal adenocarcinoma than the colon adenocarcinoma (*P*-value = 0.019 and P-value = 0/043 respectively). However, the *PVT1*expression level was not statistically significant between these colon and rectal adenocarcinoma (P-value = 0.09) (Fig. 4).

The Tumor Stage can Effect on the Expression Levels of Candidate lncRNAs

Although we could not find any statistically significant relationship between tumor stage and expression level of our candidate lncRNAs, the expression level score of *PVT1* was more in high stage tumor samples (Stage above the III) than the low grade one.

The Association of Candidate lncRNA Expression Level with Survival of Patients with Colorectal Adenocarcinoma

Considering the association of candidate lncRNAs with patient survival we found that only lncRNA *PVT1* was associated with reduced survival in patients with colorectal adenocarcinoma. We found that the over-expression of *PVT1* in colorectal adenocarcinoma was nearly associated with reduced survival to a median of 60.74 months in *PVT1* over-expressing cases, compared with the period of over

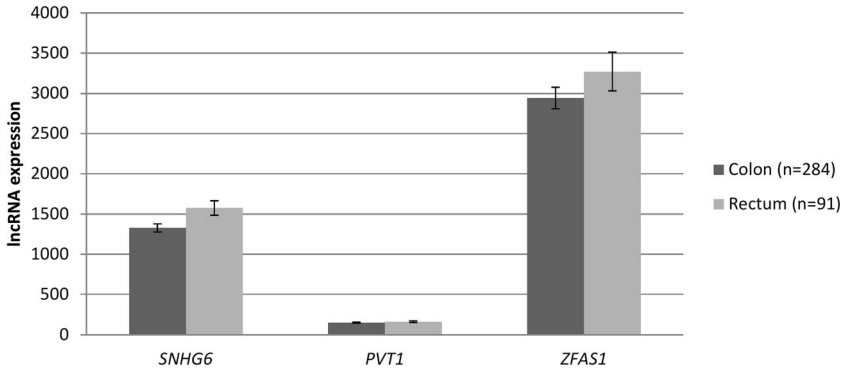

Fig. 3 The association of Tumor anatomic site with the expression levels of *SNHG6, PVT1* and *ZFAS1* lncRNAs. Data was expressed as Mean ± SD. Raw data was obtained from cBioPortal dataset

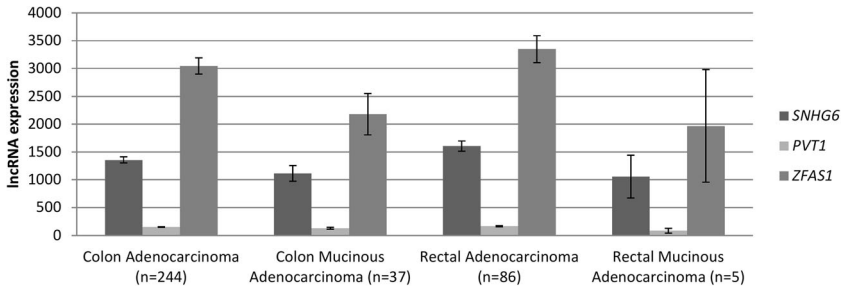

Fig. 4 The association of Neoplasm Histological type with the expression levels of *SNHG6, PVT1* and *ZFAS1* lncRNAs. Data was expressed as Mean ± SD. Raw data was obtained from cBioPortal dataset

99.93 months for the cases with no alteration in *PVT1* (Logrank Test *P*-Value: 0.058) (Fig. 5).

The Chromosomes 3q and 17q Seems to be Involved in Colorectal Carcinoma

As shown in Table 1, among 154 cases of colorectal adenomacarcioma, the lncRNA *PVT1* and *ZFAS1, as well as PVT1 and SNHG6,* have significantly tendency towards mutual exclusivity while *ZFAS1* and *SNHG6* have tendency toward co-occurrence. We found the most of the genes which are co-expressed *PVT1* has been located on 17q while the coexpressed genes of *SNHG6* and *ZFAS1* has been mostly located on 3q. As we found that *SNHG6* and *ZFAS1* have a tendency to express with each other. We also found the shared co-expressed genes of these two lncRNAs. Our data showed that the genes *CCDC58*, *AADAC*, *DNAJC19*, *ACPP*, *OTOL1*, *ACTL6A,* and *ADCY5*.

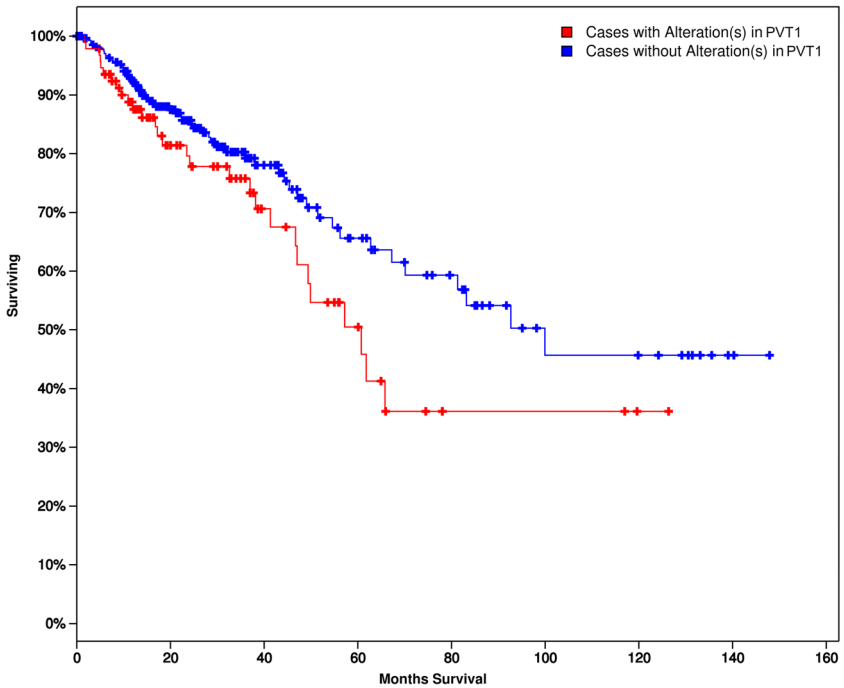

Fig. 5 Kaplan-Meier plots comparing the overall survival in cases with or without *PVT1* over-expression. The data was recruited from cBioPortal dataset

Table 1 Mutual exclusivity and co-occurrence analysis of *SNHG6*, *PVT1* and *ZFAS1* using cBioPortal dataset

GeneA	GeneB	*p*-value	Log odds ratio	Association
ZFAS1	*PVT1*	5.5e-8	−1.966	Tendency towards mutual exclusivity (Significant)
ZFAS1	*SNHG6*	0.34	0.18	Tendency towards co-occurrence
PVT1	*SNHG6*	0.47	−0.075	Tendency towards mutual exclusivity

The Specificity of Candidate lncRNAs Expression Levels in Colorectal Cancers

The transcriptomic alterations of lncRNAs *PVT1*, *ZFAS1* and *SNHG6* were considered among different human tumors. We analyzed the genes at two points; first, their frequency among the patients and second, their related mean expression among them. In comparison with *ZFAS1,* the *PVT1* and *SNHG6* were allocated a good value to itself at both levels (Fig. 6).

The lncRNA *PVT1* Sets Up a Bridge Between the Coding and Noncoding Dominions

As shown in Fig. 7, the *PVT1* can interact with variety of DNA sequences (*C-myc* and *YY1*), miRNA (*miR-15*, *miR-16*, *miR-190,...*) and protein especially transcription factors (P53 and C-myc).

Discussion

Genetic and transcriptomic alteration of lncRNAs has been recently considered in a variety of human tumors [18]. It has demonstrated that dysregulation of lncRNAs is significantly associated with cell proliferation and metastasis of colorectal cancers [9]. Here is a report studying the contribution of lncRNAs to colorectal adenocarcinoma using in silico analysis. We evaluated the expression levels of 189 approved lncRNAs in 382 samples of colorectal adenocarcinoma and found that lncRNAs *SNHG6*, *PVT1,* and *ZFAS1* had high levels of alteration. Additionally, we found that the expression of lncRNA *SNHG6* and *ZFAS1* in rectal adenocarcinoma samples were more than colon carcinoma. Besides, we found that these two lncRNAs showed a tendency towards co-occurrence in colorectal samples. Although no experimental data was found for the involvement of *SNHG6* in colorectal cancer, in

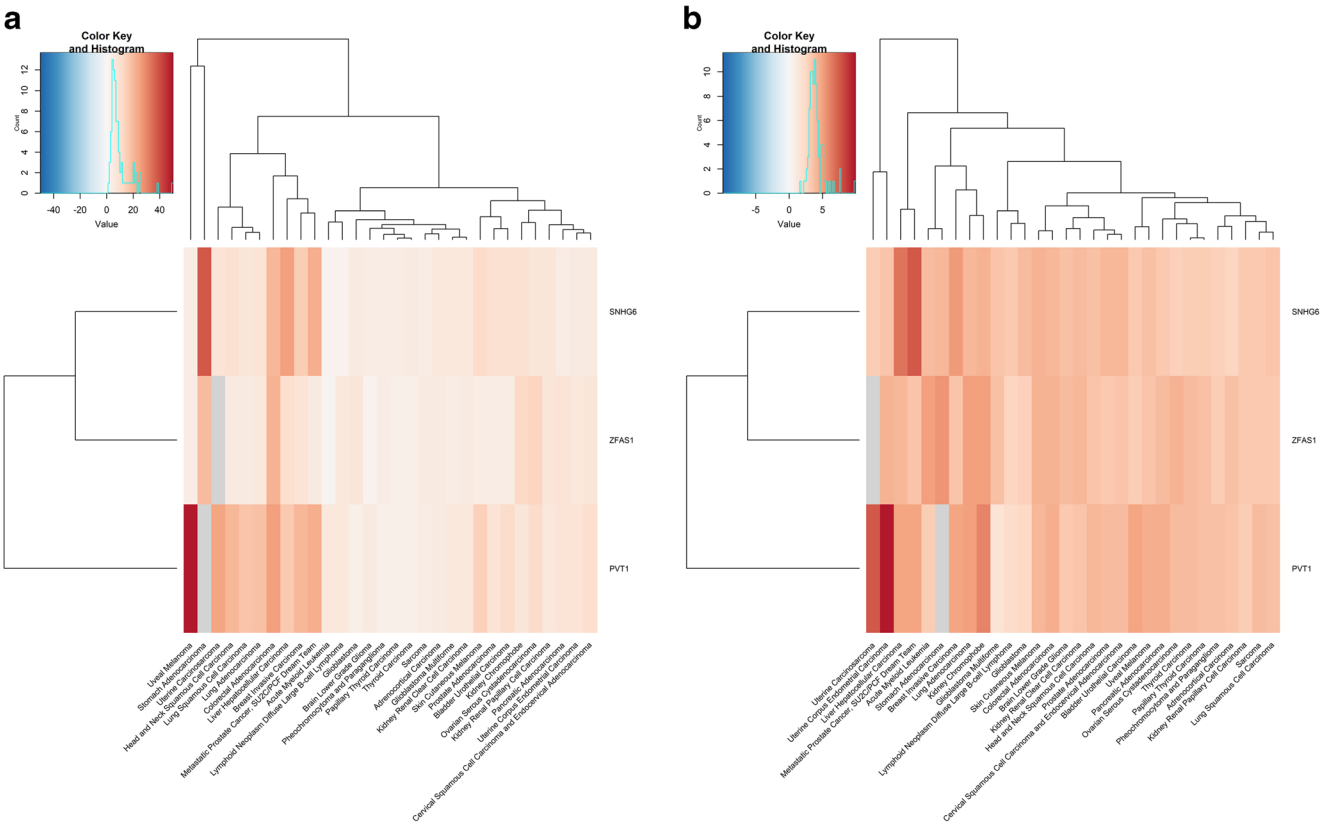

Fig. 6 The genetic alterations of *PVT1*, ZFAS1, and *SNHG6* among different human cancers. **a** The frequency of *PVT1,* ZFAS1 and *SNHG6* genetic alterations among the patients of 30 cancers with available RNA-seq on the portal. **b** The heatmap of the mean expression levels of *PVT1,* ZFAS1 and *SNHG6* among 30 cancers with RNA-seq. The heatmaps were drawn using the R software and the raw data of cBioPortal. The grey column represents cancer with no data in case of the gene of interest in the portal

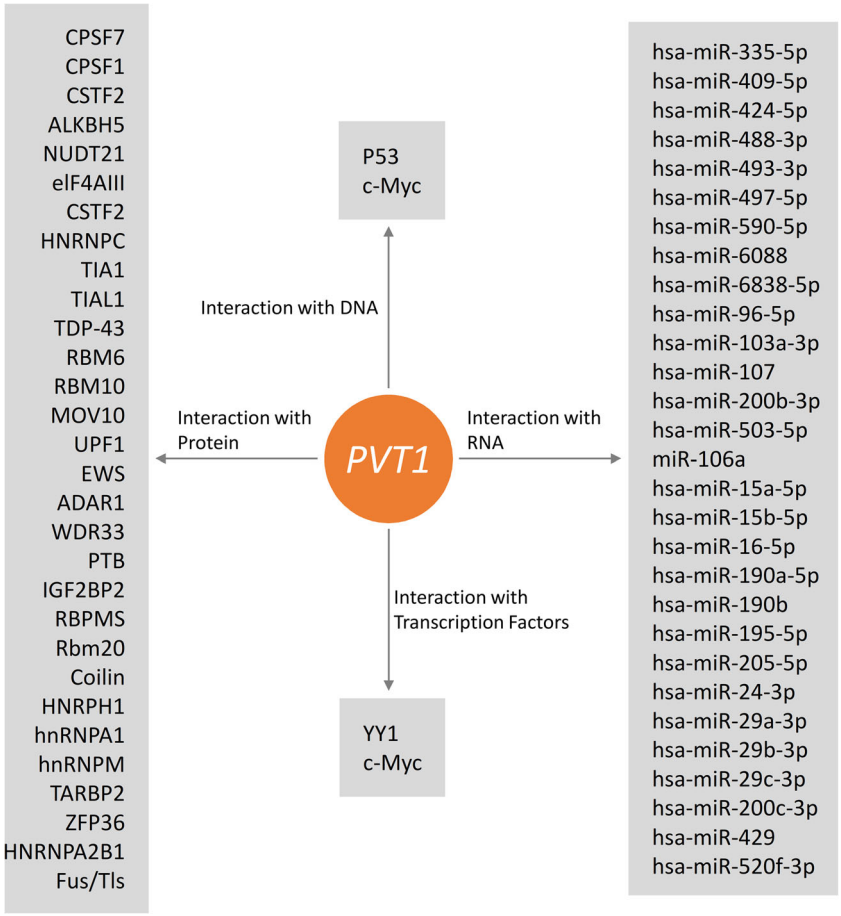

Fig. 7 Network interaction of *PVT1* lncRNA in the cells. Data has been extracted from NPInter dataset (http://www.bioinfo.org/NPInter/search.php)

case of *ZFAS1*, it has recently been found that this lncRNA can interact with constitutes of cell cycle and apoptosis pathways in colorectal samples [19]. It has also been shown that upregulation of *ZFAS1* predicts poor prognosis and stimulates invasion and metastasis in colorectal cancer [20]. We also found 7 genes (*CCDC58*, *AADAC*, *DNAJC19*, *ACPP*, *OTOL1*, *ACTL6A,* and *ADCY5*) have been significantly coexpressed with that *SNHG6* and *ZFAS1*. All of these genes have been located on Chromosome 3q. The importance of 3q in progression of colorectal cancer has been confirmed in several studies [21, 22]. We also found that lncRNA *PVT1* was associated with reduced survival in colorectal cancer cases. The expression score of *PVT1* was also very high in samples with tumor stage above the III although it was not statistically significant. This partly can be due to a small number of patients in some groups of tumor stage. In a recent publication by Guo et al., the significance of *PVT1* with progression of colorectal cancer was also confirmed [23]. We also found that most of the co-expressed genes with *PVT1* were located on 17q, a chromosomal region that has been previously introduced as a hotspot region for colorectal cancer [24]. Interestingly, we found that *PVT1* can interact with variety of DNA sequences, miRNAs and proteins especially transcription factors. Among these, P53 and C-myc were more attractive targets as *PVT1* interacted with them at both level of their coding sequences and proteins. The oncogenic role of transcription factors *P53* and *C-myc* in carcinogenesis is well-established and colorectal cancers is no exception [25–27]. Variety of miRNAs seems to be target by *PVT1* among which the role of *miR-16*, *mir-15, miR-107* and some other miRNAs has been recently reported in colorectal cancer [28–30]. These finding demonstrates that *PVT1* capable to produce a big signaling pathways to promote carcinogenesis although experimental model are needed to confirm. Finally, considering the specificity of these three candidate lncRNAs in colorectal cancer in comparison with other human cancers recorded in bioportal showed that *SNHG6* and *PVT1* were allocated the better value than *ZFAS1*. Altogether, this data introduced *SNHG6, PVT1, and ZFAS1* as good candidates for experimental works on colorectal adenocarcinoma researches. However, clinical experiments are crucial to calculate their molecular role in colorectal adenocarcinoma progression as well as its specificity and sensitivity as a biomarker of colorectal adenocarcinoma. As an example, *SNHG6* can be considered as biomarker for HCC progression [31]. This is a reason that states that how experimental job can complete the in silico analysis to decide precisely.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

It is an in silico analysis on recorded raw data on cancer bioportals.

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