Original Paper

Long Noncoding RNA BCYRN1 Promotes the Proliferation of Colorectal Cancer Cells via Up-Regulating NPR3 Expression

Lei Gu   Liesheng Lu   Donglei Zhou   Zhongchen Liu

Department of General Surgery, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai, China

Abstract

Background/Aims: Long noncoding RNAs (lncRNAs) constitute a large proportion of noncoding transcripts that have recently emerged as a new class of important regulators in cancers. LncRNA BCYRN1, also known as BC200, has a potential function in tumorigenesis. However, the clinical significance of BCYRN1 and its effect on colorectal cancer (CRC) progression remains unclear. ***Methods:*** Quantitative reverse transcriptase PCR (qRT-PCR) was performed to investigate the expression of BCYRN1 in CRC tissues and cell lines. The biological function of BCYRN1 was also investigated through knockdown and overexpression of BCYRN1 *in vitro*. Microarray bioinformatics analysis was performed to analyze the putative targets of BCYRN1. ***Results:*** The results showed that BCYRN1 expression was significantly upregulated in 96 CRC tumor tissues compared with para-carcinoma control tissues. Additionally, BCYRN1 overexpression was associated with larger tumor size and advanced pathological stages in CRC patients. *In vitro* BCYRN1 knockdown significantly inhibited the proliferation and apoptosis of CRC cells. Furthermore, NPR3 was identified to be a target of BCYRN1 and was downregulated by BCYRN1 knockdown. ***Conclusion:*** Together, we provide the first evidence that BCYRN1 plays an oncogenic role in CRC cells. BCYRN1 may be a promising prognostic biomarker and a potential therapeutic target for CRC.

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Zhongchen Liu

No. 301 Middle Yanchang Road, Shanghai Tenth People's Hospital, School of Medicine
Tongji University, Shanghai 200072 (China)
E-Mail liuzhongchen_10th@163.com

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Introduction

Colorectal cancer (CRC) is known as the third most common cancer and the fourth cause of cancer death worldwide [1-3]. An estimated 600, 000 CRC deaths occurred each year in the world, and 376, 300 cases were diagnosed in China in 2015 [4, 5]. CRC has become a severe risk to human health for its poor prognosis [6, 7]. Understanding the genetic and molecular mechanism of CRC is critical for the development of an early diagnosis and an accurate therapy for CRC.

In recent years, mounting evidence has indicated that long non-coding RNAs (lncRNAs) have been participated in the development and progression of human diseases [8-10]. LncRNAs are evolutionarily conserved ncRNAs with more than 200 nucleotides in length and no protein-coding capacity [11, 12]. Emerging evidence has shown that lncRNAs are implicated in multiple cellular biological processes, and several lncRNAs have been reported to be involved in CRC progression and tumorigenesis [13-16]. For example, lncRNA TUG1, one of the well-studied lncRNAs, is regarded as a critical diagnostic biomarker in CRC [17].

Dysregulation of lncRNA BCYRN1 has been found in various cancers, as well as in neurodegenerative diseases [18, 19]. However, the clinical role of BCYRN1 and its biological functions in CRC remains unknown. Natriuretic peptide receptor C (NPR3) is an atrial natriuretic peptide receptor, which inhibits adenylyl cyclase activity via a Gi-coupled signaling pathway. In this study, we investigated the expression and biological function of BCYRN1 in CRC. Also, we defined the clinical role of BCYRN1 in CRC.

Materials and Methods

Patients and tumor samples

CRC tumor specimens and the adjacent normal tissues were collected from 96 patients underwent resection at the Shanghai Tenth People's Hospital, Tongji University between July 2010 and December 2013. Surgically resected tissues samples were immediately frozen in RNALater (Qiagen, Hilden, Germany) and subsequently stored at −80°C until use. The clinicopathological data for histological grading, TNM staging, and lymph node status of CRC were histopathologically confirmed. The clinicopathological parameters of the CRC patients are summarized in Table 1. The study was approved by the Clinical Research and Ethics Committee at Shanghai Tenth People's Hospital, Tongji University. Written informed consents were obtained from all participants.

Table 1. Correlation between BCTRN1 and clinicopathological characteristics in 96 CRC patients. * Chi-squared test. *P<0.05

Parameters		BCTRN1		P
		High	Low	
Age (years)				0.583
>50	60	39	21	
≤50	36	24	12	
Sex				0.744
Male	61	47	14	
Female	35	25	10	
Tumor diameter (cm)				0.043*
≥5cm	34	22	12	
<5cm	62	51	11	
Location				0.305
Colon	37	26	11	
Rectum	59	44	15	
TNM stage				0.017*
I	4	4	0	
II	19	10	9	
III	27	24	3	
IV	46	35	11	
Lymphatic metastasis				0.631
Yes	44	33	11	
No	52	40	12	
Distant metastasis				0.528
Yes	12	9	3	
No	84	63	21	
Tumor differentiation				0.096
Low	25	18	7	
Middle	67	52	12	
High	4	3	1	

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Table 2. Sequence of primer and siRNA

Gene	Sense(/Antisense)	Tm	Length
GAPDH	GTGACGTTGACATCCGTAAAGA	61.6	450
	GCCGGACTCATCGTACTCC	60.3	
Cabyr	AGAGGATCACCTTGGGGTACA	61.7	98
	CGAAGCGACAGATGGTGGTC	62.9	
Pcsk4	TTGCTTACAAGGGTCTGCTACT	60.4	106
	ACTGGTAGAAGAATCAGGGCT	60.1	
My12	CCCTGAAGTCGAGGAGCTG	60.9	114
	CTGCTGCACCTCTAAGCGA	61.7	
Kng2	GAAGCGTCTCACTCCCGAAG	62.3	93
	GAAGAAAACGTCGCGCTACT	60.7	
Pla2g4b	AGAGGATCACCTTGGGGTACA	61.7	98
	CGAAGCGACAGATGGTGGTC	62.9	
Cpz	CAAACCTCAATGTGTCTCTTTGC	60.2	97
	AGAGTAAAGCCTATCTCGCTGT	60.4	
Npr3	CTTCCCTCATCCTCCTGCTAC	61.1	145
	ACAAACTGGGTAAAGGTGATGG	60.2	
Rap1a	CCAAAGCGGAGTCTCGCAT	62.4	125
	GCCTAGCATCTTGCTTAGCTC	60.6	
Dhrs9	TTGCTCCGGTAACAGCAGTG	62.4	105
	GTGGTCGCTTGTGTAGAAGGA	61.7	
Pdgfb	ATGCTGGGAAAGTCATGGAAG	60.0	201
	CGTGTTCTGGTCACGAGAGA	61.2	
BCYRN1	TAAGCTTGTAACCTGCACCCGATTCACAG	62.0	112
	TGGCAGCATACTCCTGACCATACTACCCG	62.8	
si-BCYR1	TCTGATCCGCTGTACTCTCCT	60.3	60
si-Npr3	GAGAATTTCAAGTCGTGGCGA	61.2	63

Cell lines and cell culture

Human CRC cell lines GEO, SW480, and LOVO and a normal human colon mucosal epithelial cell line NCM460 were all purchased from Shanghai Institute of Biochemistry and Cell Biology (Shanghai, China). SW480 and LOVO cells were cultured in Leibovitz's L-15 medium (L-15; Gibco) in a humidified chamber with 5% CO_2 at 37°C. NCM460 and GEO cells were maintained in Dulbecco's modified Eagle's medium (DMEM; Invitrogen) under the same conditions. All the media were containing 10% fetal bovine serum (FBS; Invitrogen) and 100 U/mL penicillin and 100 mg/mL streptomycin (Invitrogen, Shanghai, China).

qRT-PCR

Total RNA was isolated from cultured cells and patient tissues using TRIzol (Invitrogen) according to the manufacturer's instructions. Total RNA was reverse-transcribed into complementary DNA (cDNA) using a PrimeScript RT reagent kit (TaKaRa Bio Inc., Japan), and qPCR was performed using SYBR Select Master Mix (Takara, Japan) on an ABI 7900 system (Applied Biosystems, USA). The reaction conditions were as follows: 95°C for 1 min, followed by 40 cycles of 95°C for 15 sec and 60°C for 1 min. Expression levels were normalized to GAPDH, and were calculated using the comparative delta-delta CT ($2-\Delta\Delta Ct$) method. All reactions were performed in triplicates. The primer sequences are shown in Table 2.

Western blot analysis

Total protein was isolated from cells, and protein concentration was detected using a bicinchoninic acid assay (BCA) kit (Thermo Scientific, MA, USA). The protein was subjected to SDS/PAGE and transferred to a polyvinylidene difluoride membrane (Millipore, Billerica, MA, USA). After blocking with 5% nonfat milk powder in TBS-T buffer for 1 hour at room temperature (RT), the membrane was incubated with primary antibody against the target proteins overnight at 4°C, followed by incubation with appropriate HRP-conjugated secondary antibodies. The protein bands were developed with the ECL System (Millipore, Billerica, MA, USA). The assay was performed three times. Anti-β-actin (Sigma-Aldrich, USA) was used for

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an internal control. Anti-cyclinD1, anti-bcl-2, and anti-bax antibodies were purchased from Cell Signaling Technology, and anti-NPR3 antibody was acquired from Abcam.

Cell transfection

siRNA or DNA transfection was performed using lipofectamine 2000 reagent (Invitrogen, USA) according to the manufacturer's instructions. Sequences of si-RNAs (Carlsbad, California, USA) are shown in Table 1. For transient transfection, CRC cells were plated into six-well plates and transfected with BCYRN1-siRNA, NC-siRNA, pcDNA-BCYRN1, pcDNA-NPR3 or empty pcDNA vector. The expression levels of BCYRN1 and NPR3 were detected by qRT-PCR.

MTT assay and colony formation assay

Cell proliferation ability was evaluated by MTT (Roche Applied Science, Switzerland) assay at 48 h post transfection [20]. Transfected cells were seeded into 96-well plates at a density of 3×10^3/well and routinely cultured for 6 h, 24 h, 48 h, 72 h and 96 h, respectively. Colony formation was conducted according to previously published procedures [20]. The rate of colony formation was determined using the following formula: colony formation rate = (number of cells/primary number of cells) *100%

Cell cycle and apoptosis analysis

Cell cycle and apoptosis analysis were performed as described previously [20]. Double staining with annexin V and PI for apoptosis detection and single staining with PI for cell cycle analysis were conducted at 48 h post transfection. The measurements were performed in triplicate.

EdU immunoflurescence assay

At 48 h post transfection, cell proliferation was determined using 5-ethynyl-2'-deoxyuridine (EdU) immunoflurescence assay according to the manufacturer's instructions (Ribobio, Guangzhou, China). Briefly, CRC cells were seeded into 96-well plates at a density of 5×10^3/well and routinely cultured. After transfection for 48 h, the culture medium was replaced with new medium containing 50 μM EdU. With another 2 h incubation, cells were fixed with formaldehyde (4%, pH=7.4) for 30 min. After treating with 0.5% Triton X-100 for 20 min, cells were washed with PBS and counterstained with anti-EdU reagents for 30 min. Subsequently, after a 30 min incubation with 100 μL Hoechst 33342 (5 μg/mL) at RT, cells were visualized by fluorescence microscopy. The level of cell proliferation was determined using the following formula: cell proliferation = (number of EdU-positive cells/all cells) *100%.

TUNEL apoptosis assay

Apoptosis was detected using a terminal deoxynu-cleotidyl transferase dUTP nick end labeling (TUNEL) apoptosis assay kit (KeyGEN BioTECH, Nanjing, China). Cells were defined as apoptotic if the entire nuclear area of the cell was positively labeled. Apoptotic cells and bodies were counted in ten high-power fields. The apoptotic index (AI) was calculated as the percentage of positively stained cells using the following equation: AI = number of apoptotic cells/total number of nucleated cells.

Microarray expression analysis

cDNA preparation, hybridization, and data analysis were carried out using Affymetrix TM HG-U133 Plus 2.0 (Affymetrix, Santa Clara, USA) following the manufacturer's instructions. Microarray slides were scanned and pre-analyzed using GeneSpring GX (Agilent Technologies, Inc., Santa Clara, USA), followed by further normalization using Robust Multi-array Average (RMA). Then, the summarization algorithm conducts background correction. Quality control check on all samples was carried out using the principal component analysis (PCA), and correlation coefficients of each pair of arrays were displayed in visual form as a heatmap. A two-fold change in expression and a p-value < 0.05 were recognized as significantly differentially expressed genes.

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Statistical analysis

All data were presented as the mean ± standard error (S.E.M.) from at least three independent experiments. Statistical significance was assessed by two-tailed Student's *t*-test or one-way multivariate analysis of variance (ANOVA) using SPSS 19.0 statistical software (SPSS, Inc., Chicago, IL, USA). A *P* value less than 0.05 was considered statistically significant.

Results

BCYRN1 expression in CRC tissues and cell lines

We examined the expression levels of BCYRN1 in 96 CRC tissues and 96 paired adjacent normal tissues by qRT-PCR. As shown in Fig. 1A, BCYRN1 expression was significantly higher in CRC tissues than that in adjacent normal tissues (*P*=0.003). Then, we evaluated the correlation between BCYRN1 expression and clinicopathological characteristics. As shown in Fig. 1B and C, BCYRN1 expression was associated with the tumor stage (*P*=0.017) and the tumor size (*P*=0.043). To explore the biological functions of BCYRN1 in CRC progression, we knocked down BCYRN1 expression in SW480 and LOVO cells by transfection of si-BCYRN1 and enhanced BCYRN1 expression in GEO cells by transfection of pcDNA3.1-BCYRN1. BCYRN1 knockdown and ectopic expression in CRC cells were confirmed by qRT-PCR (*P*<0.01, Fig. 1D).

BCYRN1 promotes CRC cell proliferation

MTT assay results showed that BCYRN1 knockdown remarkably inhibited cell proliferation in SW480 and LOVO cells compared with control transfected cells, whereas overexpression of BCYRN1 markedly increased cell proliferation in GEO cells compared with cells transfected with vector (Fig. 2A). The clonogenic ability of CRC cells was accessed using the colony formation assay. As shown in Fig. 2B, knockdown of BCYRN1 significantly inhibited the colony formation in SW480 and LOVO cells compared with control transfected cells (*P*<0.05), whereas overexpression of BCYRN1 markedly increased the colony formation in GEO cells (*P*<0.05). These results were also confirmed by EdU/Hoechst immunostaining assay (Fig. 2C). Together, these results suggested that BCYRN1 is involved in CRC cell proliferation.

Downregulation of BCYRN1 induces G1 phase arrest and promotes apoptosis in CRC cells

To explore the potential mechanism of BCYRN1 in CRC cell proliferation, apoptosis analysis was performed using flow cytometry. The results showed that knockdown of BCYRN1 induced cell cycle arrest at G0/G1 phase (*P*<0.05, Fig. 3A). Consistently, the expression of cyclin D1 was decreased in si-BCYRN1 transfected cells compared with control cells (Fig. 3A). Moreover, we found that BCYRN1 knockdown remarkably promoted apoptosis in SW480 and
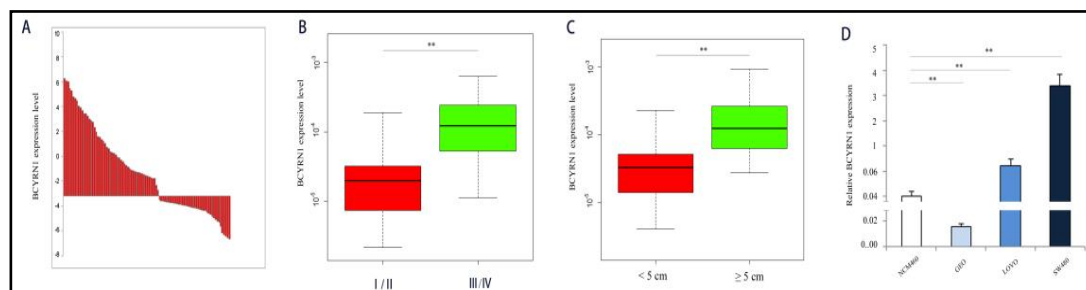

Fig. 1. Expression levels of BCYRN1 in tissues and cells. A: qRT-PCR was performed to determine the expression levels of BCYRN1 in 96 CRC tissues and 96 adjacent normal tissues. GAPDH was used as the endogenous control. B: The expression levels of BCYRN1 in tumor tissues with different pathological stage. C: The expression levels of BCYRN1 with different tumor size. D: The expression levels of BCYRN1 in different CRC cell lines compared with normal cell line. *P<0.05, **P<0.01.
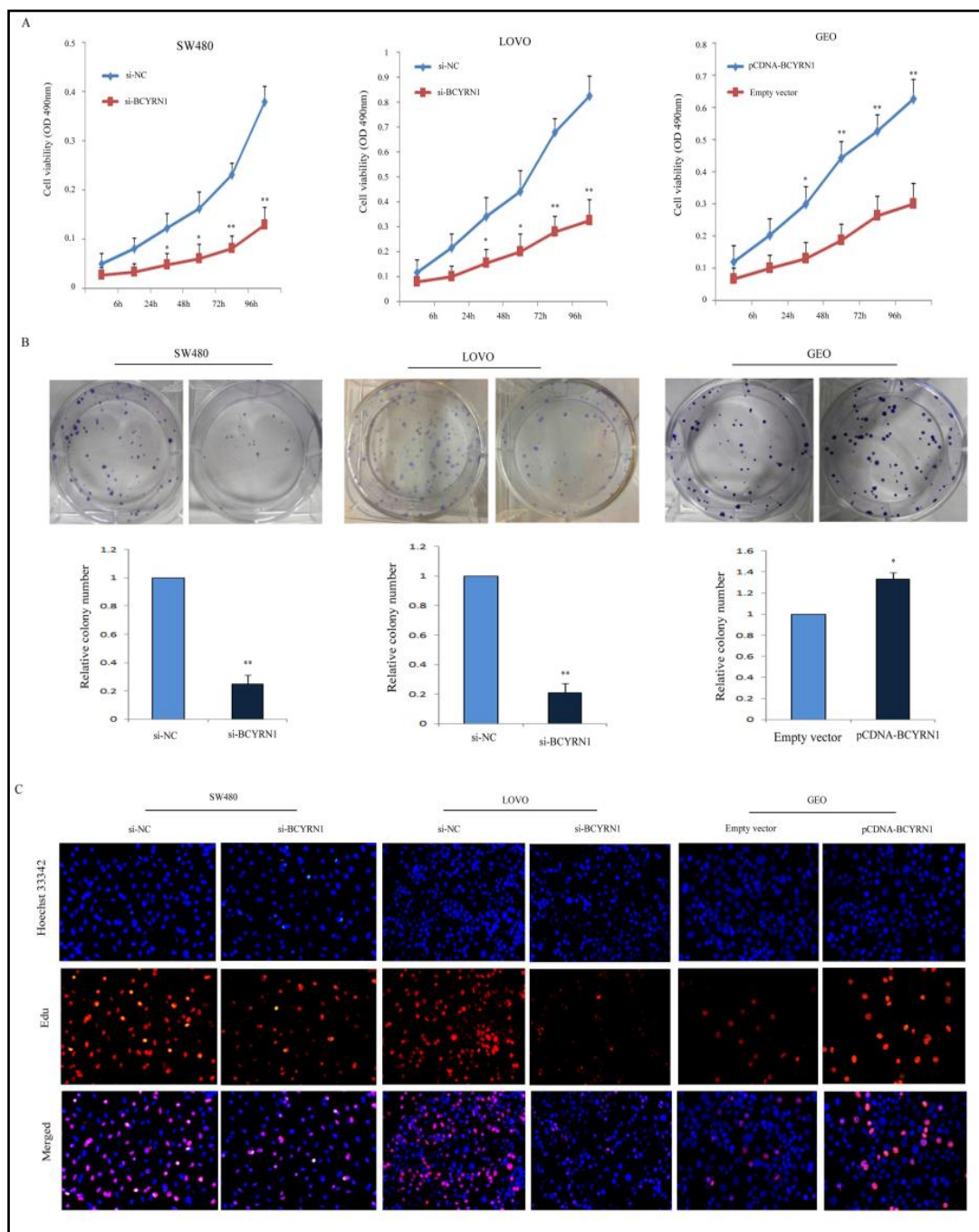
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Fig. 2. Effects of BCYRN1 on CRC cell proliferation. (A) MTT assay, (B) colony formation, and (C) EdU immunoflurescence assay were performed to determine the proliferative ability in SW480, LOVO and GEO cell lines. *P<0.05, **P<0.01. All data were presented as the mean ±S.E.M. from at least 3 independent experiments.

LOVO cells (*P*<0.05, Fig. 3B). Results from TUNEL assay also indicated that the number of TUNEL positively stained cells increased in BCYRN1 knockdown cells (Fig. 3C). In addition, Bax expression was markedly upregulated while Bcl-2 expression was downregulated in cells treated with si-BCYRN1 (Fig. 3D). These results suggested that BCYRN1 contributes to the apoptosis of CRC cells.
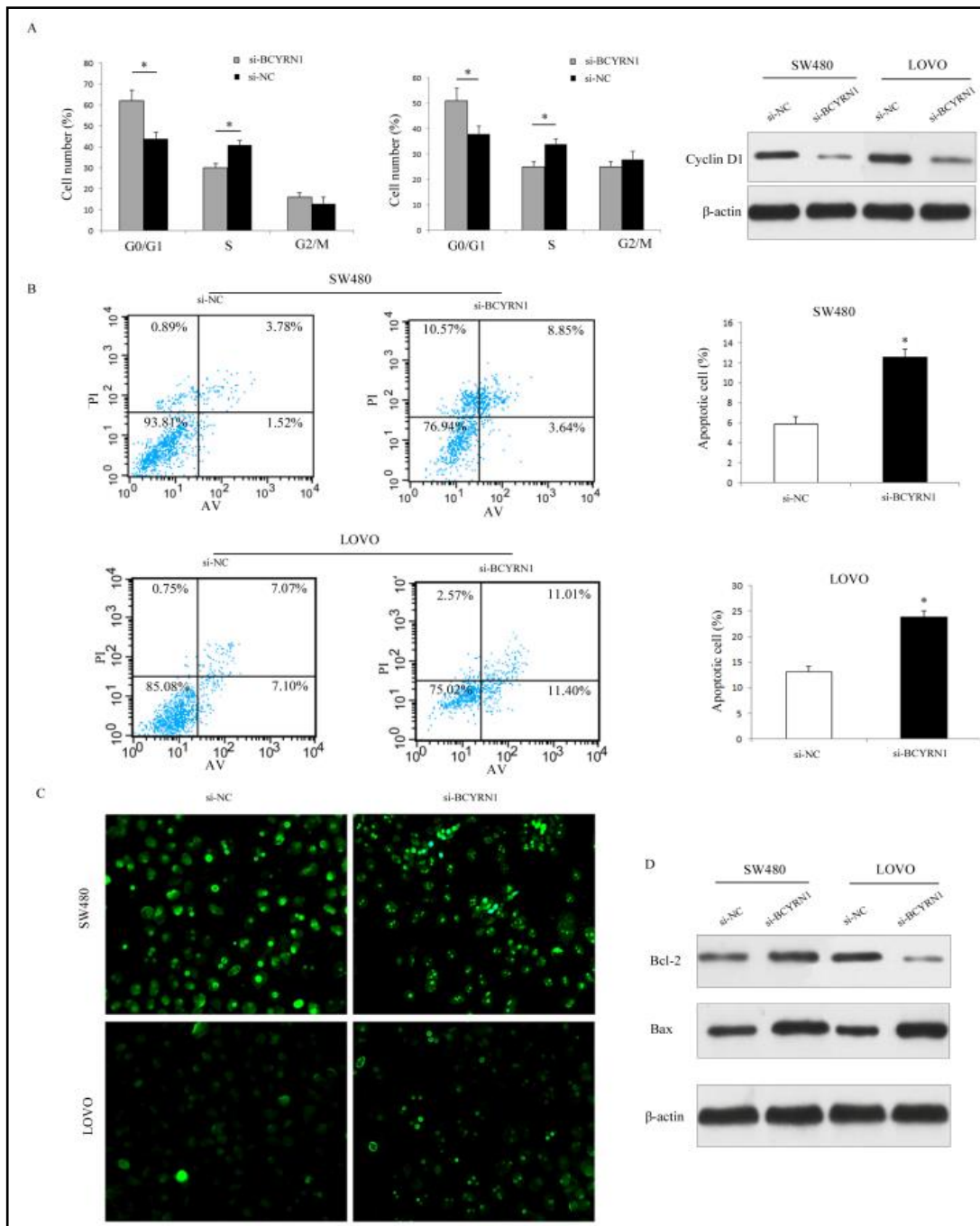
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Fig. 3. Effects of BCYRN1 on cell cycle and apoptosis of CRC cells. (A) The percentage of cells in G0/G1 phase, S phase and G2/M phase was presented in the histogram (left panel). Western blotting was carried out to detect cyclin expression in SW480 and LOVO cell lines (right panel). (B) Cell apoptosis was analyzed using flow cytometry and (C) fluorescence microscopy. (D) Western blotting was carried out to determine Bax and Bcl-2 expressions in SW480 and LOVO cell lines. *P<0.05. All data were presented as the mean ± S.E.M. from at least 3 independent experiments.

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Gene expression profiles

To identify BCYRN1 knockdown-mediated transcriptional changes, we used microarray analysis to compare the expression profiles between cases and controls. The threshold used to screen up- or down-regulated genes was Fold Change >=2.0 and p-value <=0.05 (Fig. 4A). The significantly differential expression genes were identified compared with control group. To confirm the microarray data, the top five up or down regulated genes were determined
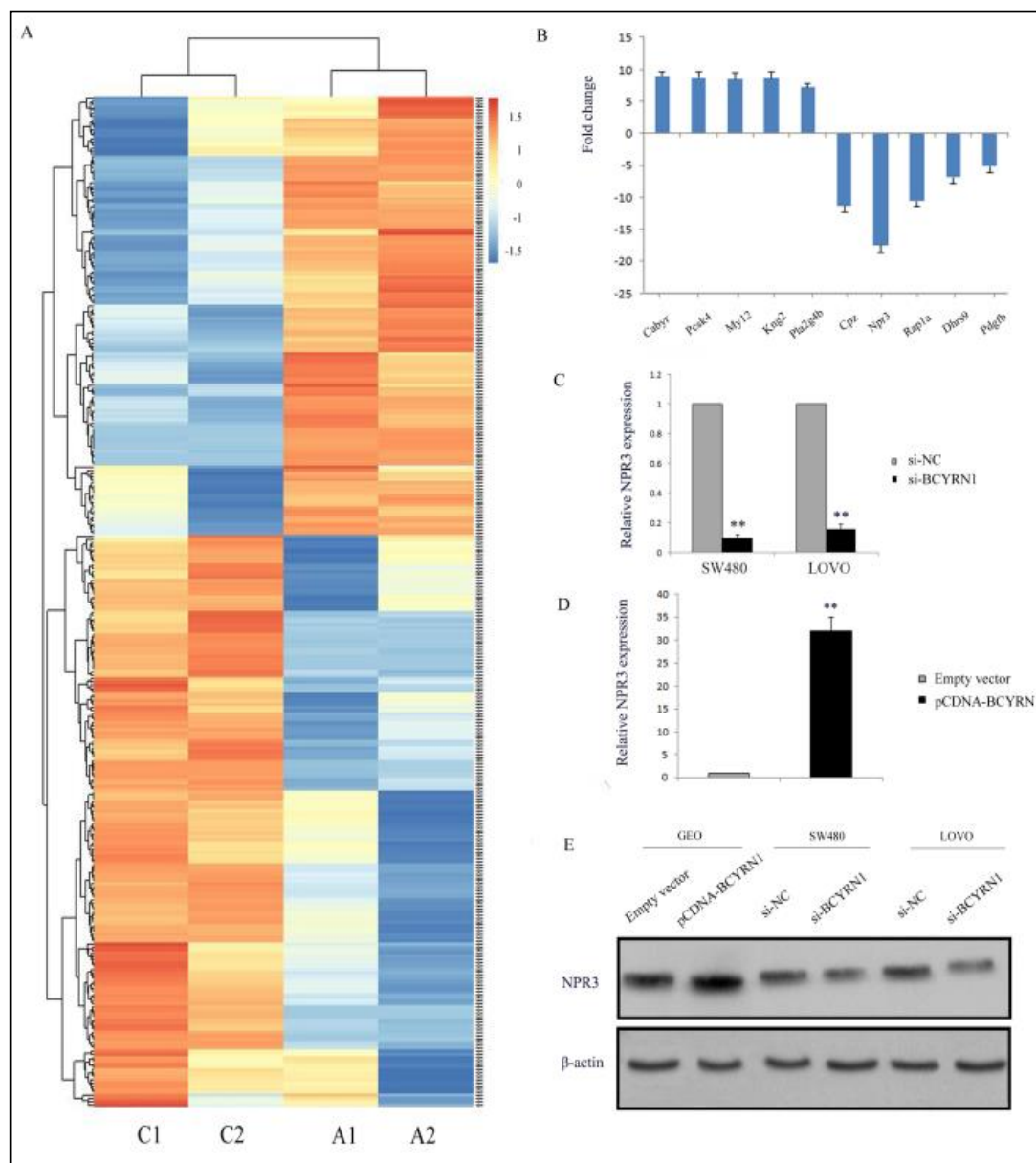

Fig. 4. Microarray expression analysis of SW480 cells with BCYRN1 knockdown. (A) Upregulated genes (orange) and downregulated genes (blue) with significantly differential expression (≥2.0-fold) were identified compared with control group. (B) qRT-PCR was performed to determine the top five up- or down-regulated genes with significantly differential expression. GAPDH was used as the endogenous control. (C) qRT-PCR was carried out to detect NPR3 expressions in SW480 and LOVO cell lines treated with control siRNA (si-NC) or si-BCYRN1. (D) qRT-PCR was carried out to detect NPR3 expressions in GEO transfected with vector or pcDNA-BCYRN1. (E) Western blotting was performed to detect NPR3 expressions in SW480, LOVO and GEO cell lines after BCYRN1 knockdown or overexpression. *P<0.05, **P<0.01. All data were presented as the mean ± S.E.M. from at least 3 independent experiments.

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using qRT-PCR (Fig. 4B). Next, we focused on NRP3, whose expression was mostly changed upon BCYRN1 alteration. We found that knockdown of BCYRN1 significantly decrease NPR3 mRNA and protein expression, whereas overexpression of BCYRN1 markedly upregulated NPR3 mRNA and protein expression (Fig. 4C-E). These results suggested that BCYRN1 could regulate NPR3 expression.
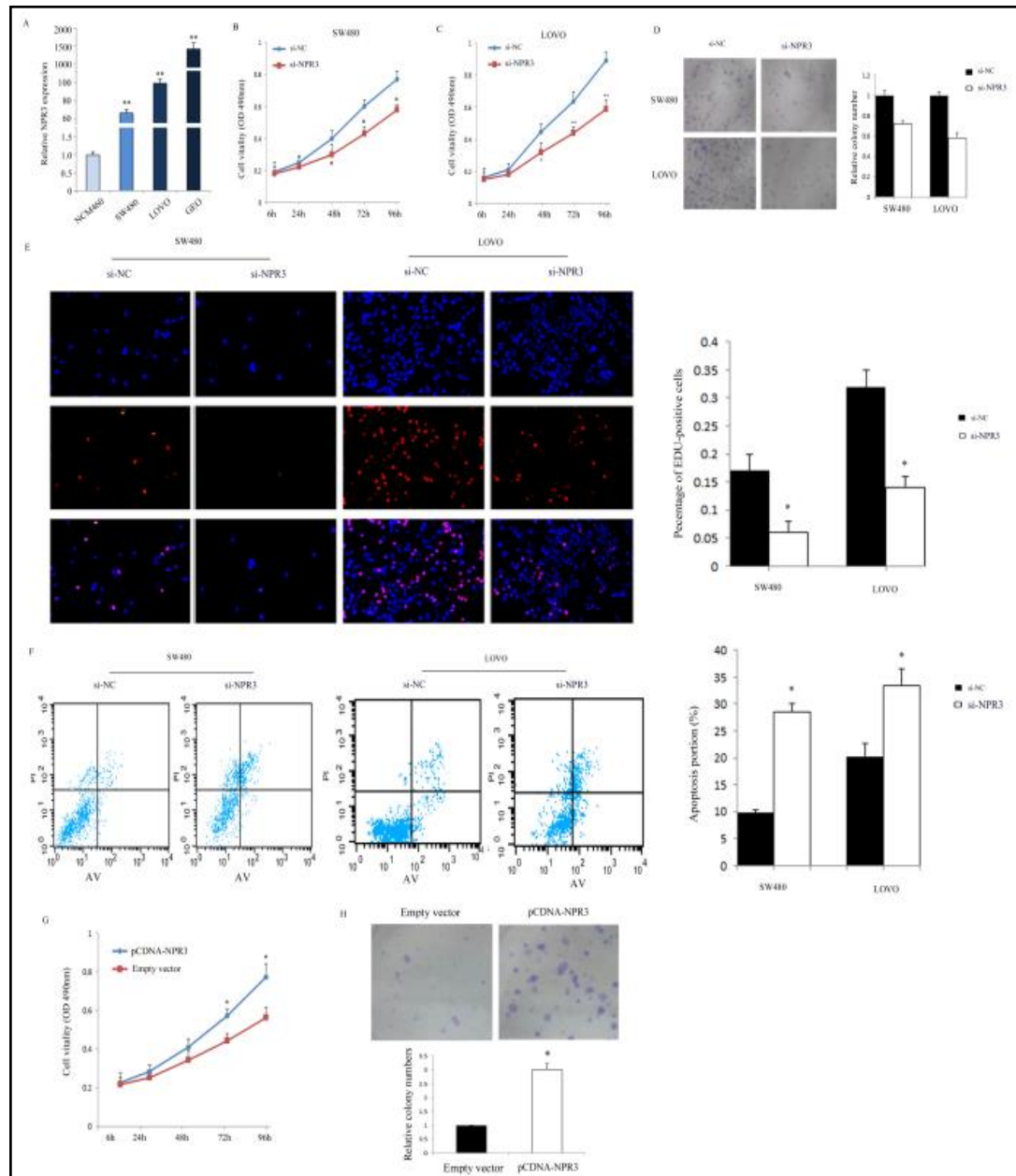

Fig. 5. Effects of BCYRN1 on the proliferation and apoptosis of CRC cells. (A) qRT-PCR was performed to determine NPR3 expressions in SW480, LOVO, GEO, and NCM460 cell lines. (B, C) MTT assay, (D) colony formation, and (E) EdU immunoflurescence assay were carried out to detect the proliferative ability of SW480 and LOVO cell lines treated with siRNA or si-NPR3. (F) Cell apoptosis was performed using flow cytometry. (G) MTT assay and (H) colony formation were performed to determine the proliferative vitality of SW480 cells thransfected with vector or pcDNA-NPR3. *P<0.05, **P<0.01. All data were presented as the mean ± S.E.M. from at least 3 independent experiments.
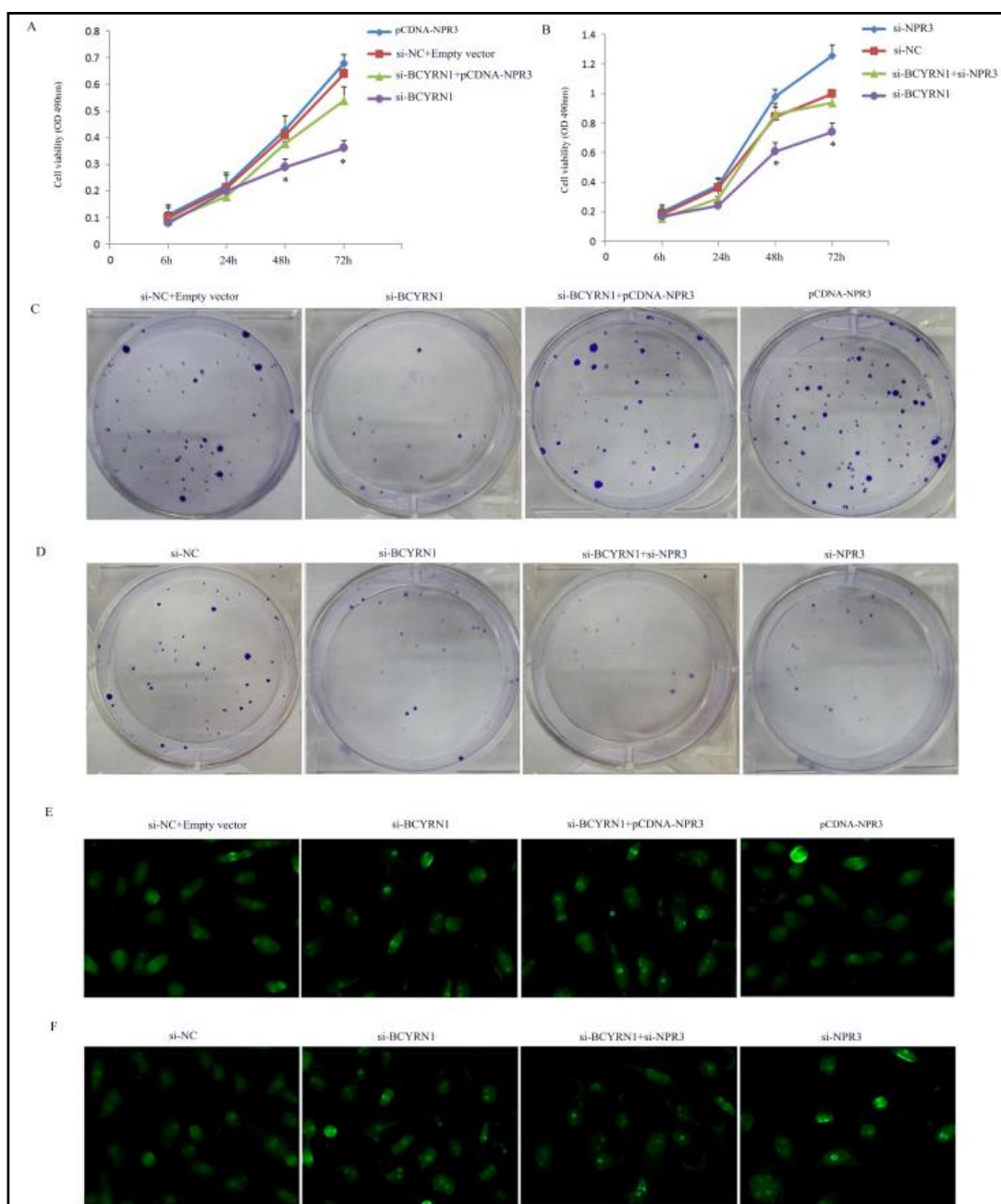
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Fig. 6. BCYRN1 promotes CRC cell proliferation through upregulation of NPR3 expression. (A) MTT assay was performed to detect the proliferation of SW480 cells transfected with siBCYRN1 alone or together with pcDNA-NRP3. (B) MTT assay was performed to detect the proliferation of SW480 cells transfected with siBCYRN1 alone or together with si-NRP3. *P<0.05, **P<0.01. (C) Colony formation assay was performed to detect the proliferation of SW480 cells transfected with siBCYRN1 alone or together with pcDNA-NRP3. (D) Colony formation assay was performed to detect the proliferation of SW480 cells transfected with siBCYRN1 alone or together with si-NRP3. (C) TUNEL assay was performed to detect the apoptosis of SW480 cells transfected with siBCYRN1 alone or together with pcDNA-NRP3. (D) TUNEL assay was performed to detect the apoptosis of SW480 cells transfected with siBCYRN1 alone or together with si-NRP3.

NPR3 promotes the proliferation and inhibits apoptosis in CRC cells

Next, we determined NRP3 expression in CRC cells and found that NPR3 expression was elevated in SW480, LOVO and GEO cell lines, compared with NCM460 cells (Fig. 5A). MTT assay showed that the proliferation viability was significantly decreased in SW480 and LOVO cell lines after NPR3 knockdown (Fig. 5B-C). Colony formation assay and immunoflurescence assay also showed that knockdown of NPR3 suppressed the proliferation of SW480 and LOVO cells (Fig. 5D-E). Moreover, NPR3 knockdown promoted apoptosis of CRC cells (Fig. 5F). In contrast, overexpression of NPR3 significantly increased cell proliferation in SW480 cells as determined by MTT assay and colony formation assay (Fig. 5G-H). These data suggested that NPR3 could promote the proliferation and inhibit apoptosis in CRC cells.

BCYRN1 promotes the proliferation and inhibits apoptosis of CRC cells via up-regulating NPR3 expression

To investigate the effect of NPR3 on BCYRN1-induced proliferation in CRC cells, co-transfection of si-BCYRN1 and pcDNA-NPR3 was performed subsequently. The results showed that the decreased proliferative ability of BCYRN1 knockdown cells was largely restored following NPR3 overexpression, while NPR3 knockdown further extended the inhibitory effect on clonogenic ability of CRC cells by BCYRN1 knockdown (Fig. 6A-D). Consistently, TUNEL apoptosis assay showed that NPR3 overexpression suppressed the influence of BCYRN1 knockdown on apoptosis (Fig. 6E), while NPR3 knockdown enhanced this effect (Fig. 6F). Together, these results indicated that BCYRN1 promotes CRC cell proliferation via upregulating NPR3.

Discussion

Recently, increasing evidence has demonstrated that four-fifth of transcription across the human genome is associated with long non-coding RNA sequences [21, 22]. However, the underlying molecular and biological functions correlated with CRC are still unclear [23]. In this study, we found that the expression of lncRNA BCYRN1 significantly upregulated in CRC tissues compared with the adjacent normal controls. Moreover, we found that BCYRN1 expression was associated with tumor size and tumor stage, indicating that BCYRN1 might be a potential prognostic biomarker for CRC. Furthermore, our data showed an increased expression of BCYRN1 in both SW480 and LOVO cell lines compared with NCM460 cells, while a decreased BCYRN1 expression existed in GEO cells. In addition, BCYRN1 knockdown inhibited the proliferative ability and induced apoptosis in SW480 and LOVO cell lines. In contrast, overexpression of BCYRN1 markedly promoted the proliferative vitality of GEO cells. Besides, we also found that BCYRN1knockdown induced G1-phase cell cycle arrest. These results indicated that BCYRN1 contributed to the proliferation and apoptosis of CRC cells.

Recently, it has been reported that abnormal expression of BCYRN1 has an impact on varieties of human cancers [19, 24, 25]. However, the regulatory mechanism of BCYRN1 is still unclear. In this study, we found that BCYRN1 knockdown leaded to downregulation in both transcriptional and translational expressions of NPR3, while overexpression of BCYRN1 had opposite effects.

Our data showed that NPR3 expression was higher in SW480 and LOVO cell lines compared with NCM460 cells. NPR3 knockdown inhibited the proliferation ability, and induced apoptosis in SW480 and LOVO cell lines. In addition, NPR3 overexpression reversed the effects of BCYRN1 knockdown on the proliferative ability and apoptosis in CRC cells. However, the detailed effect and mechanism of BCYRN1 on NPR3 are still needed further investigation.

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Conclusion

Our study found that BCYRN1 was up-regulated in CRC tissues. Increased expression of BCYRN1 was closely associated with tumor size and tumor stage. Furthermore, BCYRN1 knockdown inhibited cell proliferation and promoted cell apoptosis. These results indicated that definition of the clinical role of BCYRN1 and its biological functions in CRC may contribute to the discovery of a new diagnostic target and prognostic biomarker for CRC.

Acknowledgements

Disclosure Statement

No conflict of interests exists.

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KARGER