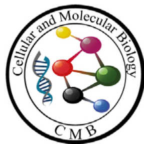

Cellular and Molecular Biology

E-ISSN : 1165-158X / P-ISSN : 0145-5680

www.cellmolbiol.org

C M B Association Publisher

LncRNA-CBR3-AS1 promotes and enhances the malignancy of ulcerative colitis via targeting miRNA-145-5p/FN1

Jingmei Cao[1],Qing Zhao[1],Qing Jia[1],Yiming Li[2*]

[1] Department of Gastroenterology, Zibo Central Hospital, Zibo, Shandong,255000, China

[2] Department of Traditional Chinese Medicine, Zibo Central Hospital, Zibo, Shandong, 255000, China

ARTICLE INFO

Original paper

Article history:

Received: May 05, 2023

Accepted: July 12, 2023

Published: July 31, 2023

Keywords:

Ulcerative colitis, LncRNA CBR3-AS1, miRNA-145-5p, FN1

ABSTRACT

Growing evidence suggested that long non-coding RNA (lncRNA) played a crucial role in the progression of ulcerative colitis (UC). Therefore, the purpose of this study is to understand how the lncRNA CBR3-AS1, which has been found to be up-regulated in UC, contributes to the bio-progression of the disease. To determine the concentration and relationship of the lncRNA CBR3-AS1, miRNA-145-5p, and FN1 in the LPS-induced Caco-2 model cells, qRT-PCR was employed in this study. Starbase was used to predict the target sites of the lncRNA CBR3-AS1 and the miRNA-145-5p, and Targetscan was used to predict the probable linking points of the FN1 and the miRNA-145-5p, which was confirmed by a twofold luciferase reporter test. The vitality of Caco-2 cells was determined using the CCK-8 and FCM tests. Using the ELISA kit, TNF, IFN, IL-6, and IL-17 were identified. The results of the experiment show that in Caco-2 cells treated with 10 ng/mL LPS, LncRNA CBR3-AS1 was up-regulated. Additionally, Caco-2 cells' LPS-induced apoptosis and inflammatory response were inhibited by lncRNA CBR3-AS1 inhibition. Dual-luciferase reporter experiments demonstrated that miRNA-145-5p and lncRNA CBR3-AS1 might connect. Moreover, miRNA-145-5p, which was shown to be poorly expressed in UC, was found to suppress inflammatory and apoptotic responses in Caco-2 cells activated by LPS. It's significant that FN1 was confirmed to be miRNA-145-5p's downstream target. Sh-CBR3-AS1's inhibitory effects were reversed by miRNA-145-5p knockdown, and the effects of the miRNA-145-5p inhibitor were reversed by sh-FN1. In conclusion, LncRNA CBR3-AS1 may offer a unique method for treating UC by suppressing the function of miRNA-145-5p, which is implicated in the development of UC.

Doi: http://dx.doi.org/10.14715/cmb/2023.69.7.29
Copyright: © 2023 by the C.M.B. Association. All rights reserved.

Introduction

UC (ulcerative colitis) is a chronic, incapacitating inflammatory bowel disease that often lasts a lifetime (1). Abdominal discomfort and diarrhea with blood and mucus are the prototypical signs of UC. Despite efforts to address it, it is still unknown how UC develops (2,3). Despite advancements in UC diagnosis and therapy, the prognosis is still dismal. Biomarker-based diagnosis and therapy have received a lot of attention lately (4). Finding the pathogenic mechanism and useful biomarkers for UC is therefore urgently needed.

Long non-coding RNA (lncRNA) is a type of essential epigenetics-regulating gene that controls DNA methylation and genomic imprinting. LncRNAs, a kind of RNA molecule longer than 200 nt but lacking the capacity to translate, have been shown to regulate tumor bio-functions such as chemotherapeutic resistance, EMT, proliferation, and more (5-8). Certain lncRNAs have been linked in several studies to the etiology of ovarian cancer, such as LncRNA PTAR, which accelerated EMT in ovarian cancer via miR-101-3p and ZEB1 (9). It has been suggested that LncRNA-BCRT1 drives the development of breast cancer (10). LncRNA CASC11 was up-regulated in bladder cancer (11). A brand-new lncRNA called CBR3-AS1 has been found to promote breast cancer cell metastasis (12). Furthermore, through Wnt/beta-catenin signaling, LncRNA CBR3-AS1 enhanced NSCLC (13). According to LncRNA CBR3-AS1 involvement in osteosarcoma (14). Although LncRNA CBR3-AS1 has been linked to several types of human cancer, its exact method of control of UC is unknown, and this is why we are interested in understanding it.

MicroRNA has a length of around 18–20 bp and is a conserved microRNA (15). certain miRNAs have been identified to have a role in the development of certain illnesses (16, 17). Recent research on miRNAs in UC has shown that some miRNAs, such as miR-31 and miR-223-3p, are crucial for the development of UC. Also, miRNA-145-5p played a role in glioma (20). However, it is yet unclear how miRNA-145-5p and associated pathways affect UC.

Extracellular matrix (ECM) protein with many domains is called fibronectin (FN1). The protein works by binding various ECM elements, including collagen, growth factors, and cell surface integrins, via its many domains (21). According to prior studies, FN1 is connected to the biological processes of several human illnesses, including head and neck squamous cell carcinoma (22), gastric adenocarcinoma (23), and others. The link between FN1 and UC has not, however, been found.

Therefore, it is beneficial to continue researching the

* Corresponding author. Email: 13969390782@163.com

pathophysiology of UC to meet the demand for innovative therapeutic approaches that have significant practical implications. In conclusion, the goal of this research is to determine if the lncRNA CBR3-AS1 modulates the UC process within the miRNA-145-5p/FN1 axis. Our research identifies Novo biomarkers that can be used to treat UC.

Materials and Methods

Cell line cultured

The ATCC provided the 293T cells and Caco-2 human colorectal cancer cells used in the Dual-luciferase test. The cells were grown in Ham's F-12k medium from Vivacell in China along with 1% penicillin and streptomycin and 20% fetal bovine serum in a 5% CO_2 environment at 37˚C.

LPS (L118716, Aladdin) was applied to Caco-2 to create an in vitro UC model. In a nutshell, Caco-2 cells were exposed to 10 ng/mL LPS for 24 hours before being collected for the tests that followed.

Bioinformatics information collected

Starbase predicted the miRNA-145-5p binding sites on the lncRNA CBR3-AS1, while TargetScan 7.0 suggested FN1 fragments with miRNA-145-5p binding sites.

Relative Dual-Luciferase reporter gene assay

To increase luciferase activity, the 3'-UTR of the lncRNA CBR3-AS1 or the mutated lncRNA CBR3-AS1 3'-UTR sequence, as well as FN1, were synthesized into a pGL3-U6-puromycin vector (Tsingke, China). After that, the 293T cells were co-transfected using jetPRIME following the supplier's instructions (Polyplus, France) with WT pGL3-lncRNA CBR3-AS1 (or FN1)-3'UTR or mutative pGL3-lncRNA CBR3-AS1 (or FN1)-3'UTR with NC mimic and mimic of miRNA-145-5p. 24 hours after infection, the activity was measured using a reporter system (Promega, USA). The outcomes have to do with Renilla luciferase.

Cell transfection

For control of expression of miRNA-145-5p, an inhibitor of miRNA-145-5p and NC inhibitor (miRNA-145-5p inhibitor: 5'-GGAAUCCCUUAGAUGCUAAGA-3' and NC inhibitor: 5'-CAAUACACCUUGUGUAGAA-CUU-3'), the mimic of miRNA-145-5p (5'-GUCCA-GUUUUCCCAGGAAUCCCU-3') and mimic NC (5'-UUCGCGGCUUAAAUGGCUUAGC-3') were purchased from Genscript (Nanjing, China). To knock down the expression of FN1, shRNA for FN1 (sh-FN1: 5'-UUAUAUCAACAAAGCUUAGGU-3') was utilized and non-specific control (sh-NC: 5'-CACGATAAGA-CAATGTATTT-3') were also purchased from Thermo Fisher (Fermantas, USA). To inhibit the expression of lncRNA CBR3-AS1, shRNA for CBR3-AS1 (sh-CBR3-AS1: 5'-GGAGAUUUAUUAUAUUCUAAU-3') was utilized and non-specific control (sh-NC: 5'-CACGATAAGA-CAATGTATTT-3') were also purchased from Thermo Fisher (Fermantas, USA). All these sequences were transfected onto cells that grew to 60% confluence with jetPRIME (Polyplus, France). After 48 h cultured at 37˚C, 5% CO_2, cells were collected after transfection.

RT-qPCR assay

Total RNA was extracted from cells using ISOLATION TRIzol buffer® (Aladdin, China), and cDNA was produced from reverse-transcribed RNA using the Titan One Tube RT-PCR kit (Merck, USA). This procedure was performed in the same manner as the supplier. TransScript® Probe SuperMix (Transgene, China) was used to measure the amount of miRNA, and PerfectStart® Sybr qPCR Mix (Transgene, Nanjing) was utilized for the qRT-PCR. By using a $2^{-\Delta\Delta Ct}$ test, the expression levels were estimated. Primers of CBR3-AS1, miRNA-145-5p, U6, FN1 and β-actin were stated below: U6: 5'-CGCCCTCTTCAG-CAGTTATACTA-3' (F) and 5'-CTTCACGCCTTTGCG-GCTCAT-3' (R); β-actin: 5'-CATGTACGTTGCTATC-CAG-3' (F) and 5'-GCGAGAGGAGCACAGATACCAC-CAA-3' (R); CBR3-AS1: 5'-CTGTCGCCCAGGCTG-GAGTGC-3' (F) and 5'-GACGCCGTGGGTCCTTCT-CATC-3' (R); miRNA-145-5p: 5'-GUCCAGTTTTCC-CAGGAAUCCCUAAACC-3' (F) and 5'-CTCAACTG-GTGTCGTGGAGT-3' (R); FN1: 5'-CGGTGGCGTC-GATCAGTCAAAG-3' (F) and 5'-ACCTCCTCGGCG-GCCTCCGCAA-3' (R).

Cell growth

The capability of cell growth was tested by the CCK-8 reagent (Solarbio, China). Caco-2 cells were resuspended and divided into 96-well plates with 5×10^3 cells after transfection and LPS stimulation. The cells were then incubated with 10 μL of the CCK-8 reagent for 1-2 hours at 37 ˚C, 5% CO_2 in the dark. Using a spectrophotometer (Bio-rad, USA), OD numerical values were found at 490 nm.

Tunel staining

The fixed cell was made into slides. The slides were cleaned before being exposed to a 50 mL TUNEL reaction mixture for 60 minutes in complete darkness in a damp box at 37 ℃. The slides were exposed to 50 mL of peroxidase for 30 min at 37 ℃. After being cleaned with PBS, the slides were incubated for 10 minutes at 25 ℃ with a 50 mL solution of diaminobenzidine substrate. Finally, a fluorescence microscope was used to look at the slides.

Enzyme-linked immunosorbent analysis

The levels of the inflammatory cytokines TNF-α, IFN-γ, IL-6, as well as IL-17 were measured in the supernatant. R&D (Bio-techne, USA) provided the ELISA kit. The supplier's instructions were followed in all processes.

Statistical analysis

The results from the triple experiments are shown as the average ± standard deviation (SD). Tukey's multiple-comparison test is used for multi-group data, whereas the student t-test is used for two groups. Statistics is considered significant if $P < 0.05$.

Results

CBR3-AS1 is down-regulated in UC

The study investigated CBR3-AS1's impact on UC because of its important role in a variety of disorders. We used RT-qPCR to examine the amount of CBR3-AS1 expression in UC. Results showed that CBR3-AS1 was highly expressed in Caco-2 cells treated with 10 ng/ml LPS (Figure 1A). In contrast to the sh-NC group, CBR3-AS1 was expressed at a lower level in Caco-2 cells trans-

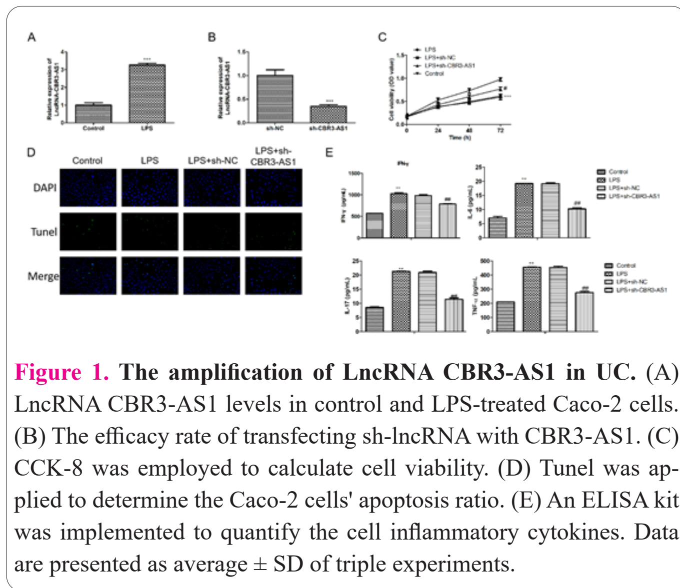

Figure 1. The amplification of LncRNA CBR3-AS1 in UC. (A) LncRNA CBR3-AS1 levels in control and LPS-treated Caco-2 cells. (B) The efficacy rate of transfecting sh-lncRNA with CBR3-AS1. (C) CCK-8 was employed to calculate cell viability. (D) Tunel was applied to determine the Caco-2 cells' apoptosis ratio. (E) An ELISA kit was implemented to quantify the cell inflammatory cytokines. Data are presented as average ± SD of triple experiments.

fected with sh-CBR3-AS1, as shown in Figure 1B. The vitality was measured by CCK-8, and the findings showed that transfection of sh-CBR3-AS1 improved cell growth whereas LPS dramatically inhibited cell proliferation (Figure 1C). In addition, the Tunel assay demonstrated that down-regulated CBR3-AS1 suppressed the ratio of cells that underwent apoptosis, which was induced by LPS (Figure 1D). TNF-α, IFN-γ, IL-6, as well as IL-17, were all significantly increased by LPS and decreased by the sh-CBR3-AS1 transfected cells (Figure 1E). Collectively, CBR3-AS1 participated in the UC process.

miRNA-145-5p bounds with CBR3-AS1

Using bioinformatics prediction tools (StarBase), we investigated the potential binding sites of CBR3-AS1 and miRNA-145-5p and found that these sites were present in miRNA-145-5p (Figure 2A). The relationship between CBR3-AS1 and miRNA-145-5p was verified using a dual-luciferase gene assay in 293T cells. When the cells were co-cultured with a mimic of miRNA-145-5p, as shown in Figure 2B, the relative luciferase expression of the CBR3-AS1 3′-UTR was noticeably decreased. The miRNA-145-5p mimic had no impact when the possible connecting sites were mutative. According to the results of RT-qPCR,

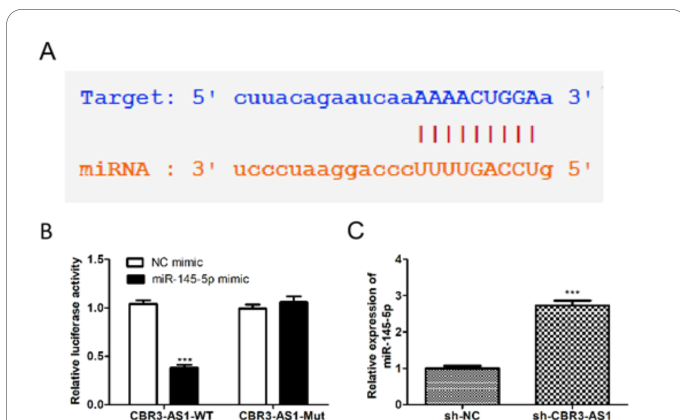

Figure 2. The miRNA-145-5p target of lncRNA CBR3-AS1. (A) The miRNA-145-5p combination locations on CBR3-AS1 WT and Mut. (B) The luciferase reporter activity of co-transfected CBR3-AS1 WT and Mut with miRNA-145-5p. (C) RT-qPCR was utilized to measure the expression level of miRNA-145-5p. Data are presented as average ± SD of triple experiments.

sh-CBR3-AS1 transfection of Caco-2 cells increased the amount of miRNA-145-5p (Figure 2C). Therefore, these findings suggest that CBR3-AS1 controls miRNA-145-5p in Caco-2 cells in an opposing manner.

miRNA-145-5p is down-regulated in UC

By using RT-qPCR to determine the amount of miRNA-145-5p, it was shown that LPS-treated Caco-2 cells had lower levels of miRNA-142-5p (Figure 3A). MiRNA-145-5p mimic transfected into Caco-2 cells led to greater expression of miRNA-145-5p compared to the NC mimic group (Figure 3B). CCK-8 was used to measure vitality, and the findings showed that LPS greatly inhibited cell growth, whereas transfection of a miRNA-145-5p mimic could partially restore cell growth (Figure 3C). The Tunel experiment, in the meantime, demonstrated that up-regulated miRNA-145-5p unmistakably decreased the cell apoptosis ratio that was amplified by LPS (Figure 3D). TNF-, IFN-, IL-6, and IL-17 levels were all markedly elevated by LPS and decreased by the transfected miRNA-145-5p mimic (Figure 3E).

FN1 is downstream of miRNA-145-5p

The possible miRNA-145-5p bind sites in FN1 were discovered when we utilized Targetscan 7.0 to query the

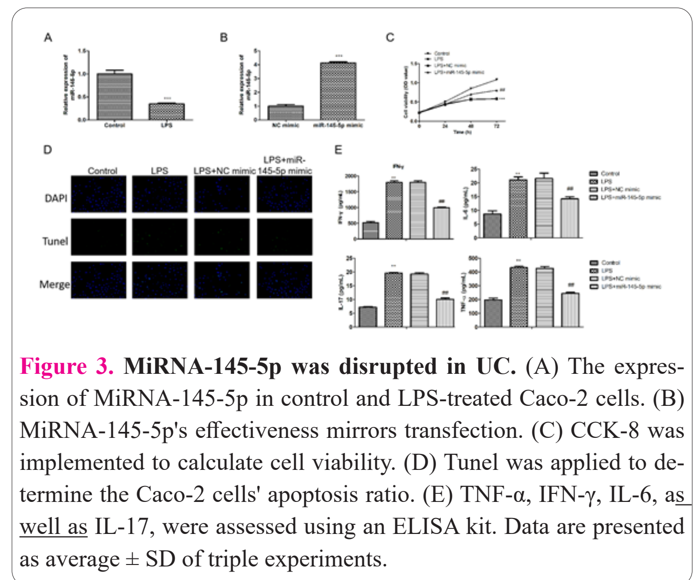

Figure 3. MiRNA-145-5p was disrupted in UC. (A) The expression of MiRNA-145-5p in control and LPS-treated Caco-2 cells. (B) MiRNA-145-5p's effectiveness mirrors transfection. (C) CCK-8 was implemented to calculate cell viability. (D) Tunel was applied to determine the Caco-2 cells' apoptosis ratio. (E) TNF-α, IFN-γ, IL-6, as well as IL-17, were assessed using an ELISA kit. Data are presented as average ± SD of triple experiments.

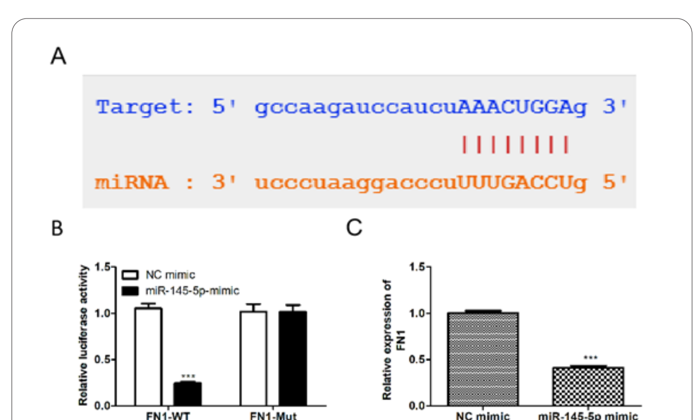

Figure 4. FN1 is miRNA-145-5p downstream mRNA. (A) Targetscan 7.0 predicted the binding sites between miRNA-145-5p and FN1. (B) The correlation between miRNA-145-5p and FN1 was confirmed using the dual relative luciferase assay. (C) FN1 expression levels were measured by RT-qPCR. Data are presented as average ± SD of triple experiments.

downstream mRNA of the miRNA (Figure 4A). To address this issue, we carried out a dual relative luciferase approach. We showed that miRNA-145-5p overexpression decreased the luciferase output of the FN1-WT reporter gene (Figure 4B). In Caco-2 cells transfected with miRNA-145-5p mimic, the FN1 expression level was affected, according to RT-qPCR results (Figure 4C). As a consequence, our findings suggest that miRNA-145-5p controls the FN1 in Caco-2 cells in an opposing manner.

miRNA-145-5p/FN1 axis participated in the impact of CBR3-AS1 silenced on UC cells

We co-cultured Caco-2 with sh-CBR3-AS1, sh-CBR3-AS1 with miRNA-145-5p inhibitor, or combination with sh-FN1 to ensure the connection of miRNA-145-5p, FN1, and CBR3-AS1 in UC. In Caco-2 cells treated with LPS, FN1 was highly expressed (Figure 5A). By transfecting sh-FN1 and miRNA-145-5p inhibitors, respectively, FN1 and miRNA-145-5p were reduced (Figure 5B). The viability of LPS-treated Caco-2 cells that were transfected with sh-CBR3-AS1+miRNA-145-5p inhibitor+sh-FN1 was higher than that treated with sh-CBR3-AS1+miRNA-145-5p inhibitor (Figure 5C). However, inhibition of CBR3-AS1 restored the viability of LPS-stimulated Caco-2 cells, whereas co-transfection of miRNA-145-5p inhibitor was reversed completely. Apoptosis was inhibited by the transfection of sh-CBR3-AS1 into LPS-treated Caco-2 cells, whereas the co-transfection of the miRNA-145-5p inhibitor increased the percentage of apoptotic cells. The co-transfection of sh-FN1 reversed the above finding (Figure 5D). Tunel demonstrated that LPS enhanced cell apoptotic rate. TNF-α, IFN-γ, IL-6, as well as IL-17 levels, were all noticeably increased by LPS and decreased by the sh-CBR3-AS1 transfection. The above-mentioned effects were subsequently reversed by down-regulating FN1 (Figure 5E).

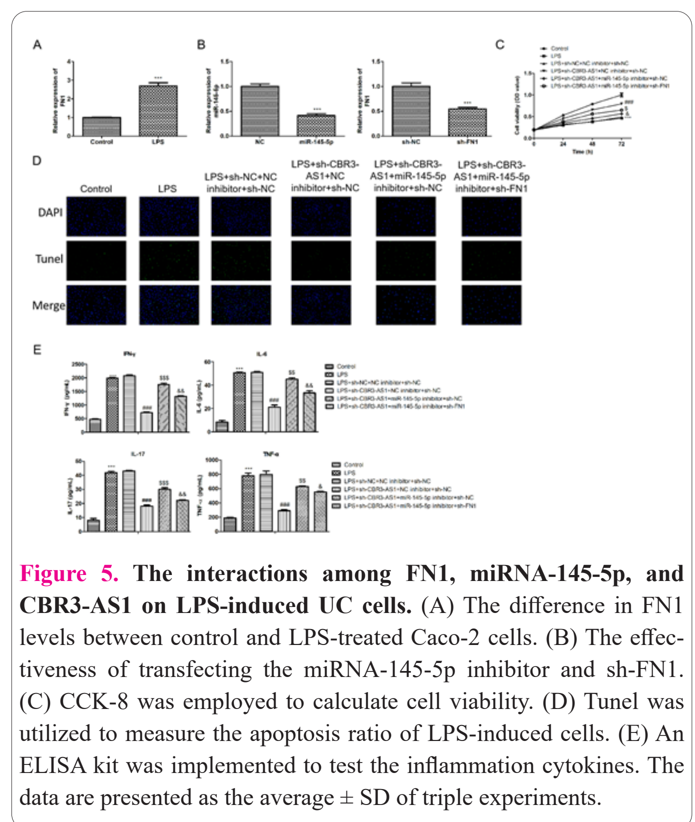

Figure 5. The interactions among FN1, miRNA-145-5p, and CBR3-AS1 on LPS-induced UC cells. (A) The difference in FN1 levels between control and LPS-treated Caco-2 cells. (B) The effectiveness of transfecting the miRNA-145-5p inhibitor and sh-FN1. (C) CCK-8 was employed to calculate cell viability. (D) Tunel was utilized to measure the apoptosis ratio of LPS-induced cells. (E) An ELISA kit was implemented to test the inflammation cytokines. The data are presented as the average ± SD of triple experiments.

Discussion

The intestinal mucosa is affected by inflammation and ulcerative alterations in UC, a chronic non-specific IBD. The mucosa, colonic submucosa, and rectum have all experienced the majority of the stress from UC. Uncertainty surrounds the pathophysiology of UC, though. According to some arguments, one key cause of UC is an immune system malfunction. Immunosuppressants, aminosalicylates, and corticosteroids are often used in clinical therapy of UC (24–26).

In this study, we outlined the molecular mechanism by which sh-lncRNA CBR3-AS1 alleviated UC that was induced by LPS. This analysis demonstrated that lncRNA CBR3-AS1 contributed to the development of UC via miRNA-145-5p, indicating that lncRNA CBR3-AS1 acted as a new UC biomarker.

More proof was found to support the idea that lncRNAs were important in UC. Different lncRNAs have been classified as biomarkers in UC. LncRNA MALAT1 and ANRIL both take part in the UC process concurrently (27). Yang W discovered that the PI3K pathway was used by lncRNA H19 to control UC (28). The lncRNA NORAD was also up-regulated in UC and used NF-κB to induce inflammation (29). However, just a little amount of study has been done to analyze the function of the lncRNA CBR3-AS1 in UC. Our research showed that the lncRNA CBR3-AS1 was promoted in UC. These discoveries improved our understanding of the role of the lncRNA CBR3-AS1 in the regulation of UC, which may help us find the pathogenic mechanism of UC more effectively.

Numerous studies have shown how miRNAs and circRNAs controlled the development of illnesses (30, 31). Forerunners discovered many miRNAs to be implicated in UC (32). Pierdomenico M discovered that miR-320 was connected to UC (33). By triggering an immunological response, Singh U. *et al.* demonstrated that miR-155 protected UC (34). On the other hand, miR-133a was shown to suppress UC (35). Since they have verified link sites, experimental evidence here established miRNA-145-5p as the lncRNA CBR3-AS1's downstream gene. We explained that the level of lncRNA CBR3-AS1 in UC was contrast-controlled with the level of miRNA-145-5p, which was down-regulated.

FN1 has previously been linked to human disorders such as renal fibrosis (38), spondylometaphyseal dysplasia (37), and oral squamous cell carcinoma (36). Additionally, FN1 was shown to be strongly expressed in UC and to be regulated by miRNA-145-5p in this study.

In conclusion, our research confirms that miRNA-145-5p/FN1 is modulated by lncRNA CBR3-AS1 to aid in the UC process. Our findings show that the lncRNA CBR3-AS1/miRNA-145-5p/FN1 offers a fresh approach to treating ulcerative colitis.

Declaration

Conflicts of interest

The authors declare that they have no conflicts of interest.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Author Contributions Statement

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Jingmei Cao, Qing Zhao, and Qing Jia. The first draft of the manuscript was written by Jingmei Cao and Yiming Li, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable.

References

1. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. Lancet 2017 J;389(10080):1756-1770. doi:10.1016/S0140-6736(16)32126-2
2. Chu H, Khosravi A, Kusumawardhani IP, Kwon AH, Vasconcelos AC, Cunha LD, Mayer AE, Shen Y, Wu WL, Kambal A, Targan SR, Xavier RJ, Ernst PB, Green DR, McGovern DP, Virgin HW, Mazmanian SK. Gene-microbiota interactions contribute to the pathogenesis of inflammatory bowel disease. Science 2016 J;352(6289):1116-1120. doi:10.1126/science.aad9948
3. Li M, Wang B, Sun X, Tang Y, Wei X, Ge B, Tang Y, Deng Y, He C, Yuan J, Li X. Upregulation of Intestinal Barrier Function in Mice with DSS-Induced Colitis by a Defined Bacterial Consortium Is Associated with Expansion of IL-17A Producing Gamma Delta T Cells. Front Immunol 2017 J;8:824. doi: 10.3389/fimmu.2017.00824.
4. Pope JL, Bhat AA, Sharma A, Ahmad R, Krishnan M, Washington MK, Beauchamp RD, Singh AB, Dhawan P. Claudin-1 regulates intestinal epithelial homeostasis through the modulation of Notch-signalling. Gut 2014 J;63(4):622-634. doi:10.1136/gutjnl-2012-304241
5. He H, Wang Y, Ye P, Yi D, Cheng Y, Tang H, Zhu Z, Wang X, Jin S. Long noncoding RNA ZFPM2-AS1 acts as a miRNA sponge and promotes cell invasion through regulation of miR-139/GDF10 in hepatocellular carcinoma. J Exp Clin Cancer Res 2020 J;39(1):159. doi:10.1186/s13046-020-01664-1
6. Tan DSW, Chong FT, Leong HS, Toh SY, Lau DP, Kwang XL, Zhang X, Sundaram GM, Tan GS, Chang MM, Chua BT, Lim WT, Tan EH, Ang MK, Lim TKH, Sampath P, Chowbay B, Skanderup AJ, DasGupta R, Iyer NG. Long noncoding RNA EGFR-AS1 mediates epidermal growth factor receptor addiction and modulates treatment response in squamous cell carcinoma. Nat Med 2017 J;23(10):1167-1175. doi:10.1038/nm.4401
7. Xu Y, Ge Z, Zhang E, Zuo Q, Huang S, Yang N, Wu D, Zhang Y, Chen Y, Xu H, Huang H, Jiang Z, Sun L. The lncRNA TUG1 modulates proliferation in trophoblast cells via epigenetic suppression of RND3. Cell Death Dis 2017 J;8(10):e3104. doi:10.1038/cddis.2017.503
8. Yuan JH, Yang F, Wang F, Ma JZ, Guo YJ, Tao QF, Liu F, Pan W, Wang TT, Zhou CC, Wang SB, Wang YZ, Yang Y, Yang N, Zhou WP, Yang GS, Sun SH. A long noncoding RNA activated by TGF-β promotes the invasion-metastasis cascade in hepatocellular carcinoma. Cancer Cell 2014 J;25(5):666-681. doi:10.1016/j.ccr.2014.03.010
9. Liang H, Yu T, Han Y, Jiang H, Wang C, You T, Zhao X, Shan H, Yang R, Yang L, Shan H, Gu Y. LncRNA PTAR promotes EMT and invasion-metastasis in serous ovarian cancer by competitively binding miR-101-3p to regulate ZEB1 expression. Mol Cancer 2018 J;17(1):119. doi:10.1186/s12943-018-0870-5
10. Han G, Guo Q, Ma N, Bi W, Xu M, Jia J, Wang W. LncRNA BCRT1 facilitates osteosarcoma progression via regulating miR-1303/FGF7 axis. Aging (Albany NY) 2021 J;13(11):15501-15510. doi:10.18632/aging.203106
11. Luo H, Xu C, Le W, Ge B, Wang T. lncRNA CASC11 promotes cancer cell proliferation in bladder cancer through miRNA-150. J Cell Biochem 2019 J;120(8):13487-13493. doi:10.1002/jcb.28622
12. Torkashvand S, Basi A, Ajdarkosh H, Rakhshani N, Nafisi N, Mowla SJ, Moghadas A, Mohammadipour M, Karbalaie Niya MH. Long Non-Coding RNAs Expression in Breast Cancer: CBR3-AS1 LncRNA as a Sensitive Biomarker. Asian Pac J Cancer Prev 2021 J;22(9):2897-2902. doi:10.31557/APJCP.2021.22.9.2897
13. Hou M, Wu N, Yao L. LncRNA CBR3-AS1 potentiates Wnt/β-catenin signaling to regulate lung adenocarcinoma cells proliferation, migration and invasion. Cancer Cell Int 2021 J;21(1):36. doi:10.1186/s12935-020-01685-y
14. Zhang Y, Meng W, Cui H. LncRNA CBR3-AS1 predicts unfavorable prognosis and promotes tumorigenesis in osteosarcoma. Biomed Pharmacother 2018 J;102:169-174. doi:10.1016/j.biopha.2018.02.081
15. Shi Y, Fang N, Li Y, Guo Z, Jiang W, He Y, Ma Z, Chen Y. Circular RNA LPAR3 sponges microRNA-198 to facilitate esophageal cancer migration, invasion, and metastasis. Cancer Sci 2020 J;111(8):2824-2836. doi:10.1111/cas.14511
16. Bandiera S, Pfeffer S, Baumert TF, Zeisel MB. miR-122--a key factor and therapeutic target in liver disease. J Hepatol 2015 J;62(2):448-457. doi:10.1016/j.jhep.2014.10.004
17. Elton TS, Selemon H, Elton SM, Parinandi NL. Regulation of the MIR155 host gene in physiological and pathological processes. Gene 2013 J;532(1):1-12. doi:10.1016/j.gene.2012.12.009
18. Tian Y, Xu J, Li Y, Zhao R, Du S, Lv C, Wu W, Liu R, Sheng X, Song Y, Bi X, Li G, Li M, Wu X, Lou P, You H, Cui W, Sun J, Shuai J, Ren F, Zhang B, Guo M, Hou X, Wu K, Xue L, Zhang H, Plikus MV, Cong Y, Lengner CJ, Liu Z, Yu Z. MicroRNA-31 Reduces Inflammatory Signaling and Promotes Regeneration in Colon Epithelium, and Delivery of Mimics in Microspheres Reduces Colitis in Mice. Gastroenterology 2019 J;156(8):2281-2296.e6. doi:10.1053/j.gastro.2019.02.023
19. Wu X, Pan S, Luo W, Shen Z, Meng X, Xiao M, Tan B, Nie K, Tong T, Wang X. Roseburia intestinalis-derived flagellin ameliorates colitis by targeting miR-223-3p-mediated activation of NLRP3 inflammasome and pyroptosis. Mol Med Rep 2020 J;22(4):2695-2704. doi:10.3892/mmr.2020.11351
20. Chen J, Chen T, Zhu Y, Li Y, Zhang Y, Wang Y, Li X, Xie X, Wang J, Huang M, Sun X, Ke Y. circPTN sponges miR-145-5p/miR-330-5p to promote proliferation and stemness in glioma. J Exp Clin Cancer Res 2019 J;38(1):398. doi:10.1186/s13046-019-1376-8
21. Zollinger AJ, Smith ML. Fibronectin, the extracellular glue. Matrix Biol 2017 J;60-61:27-37. doi:10.1016/j.matbio.2016.07.011
22. Liu X, Meng L, Li X, Li D, Liu Q, Chen Y, Li X, Bu W, Sun H. Regulation of FN1 degradation by the p62/SQSTM1-dependent autophagy-lysosome pathway in HNSCC. Int J Oral Sci 2020 J;12(1):34. doi:10.1038/s41368-020-00101-5
23. Li L, Zhu Z, Zhao Y, Zhang Q, Wu X, Miao B, Cao J, Fei S. FN1, SPARC, and SERPINE1 are highly expressed and significantly related to a poor prognosis of gastric adenocarcinoma revealed by microarray and bioinformatics. Sci Rep 2019 J;9(1):7827. doi:10.1038/s41598-019-43924-x
24. Lord JD. Promises and paradoxes of regulatory T cells in inflammatory bowel disease. World J Gastroenterol 2015 J;21(40):11236-11245. doi:10.3748/wjg.v21.i40.11236
25. Liu Y, Zhang XJ, Yang CH, Fan HG. Oxymatrine protects rat brains against permanent focal ischemia and downregulates NF-kappaB expression. Brain Res 2009 J;1268:174-180. doi:10.1016/j.brainres.2009.02.069

26. Hong-Li S, Lei L, Lei S, Dan Z, De-Li D, Guo-Fen Q, Yan L, Wen-Feng C, Bao-Feng Y. Cardioprotective effects and underlying mechanisms of oxymatrine against Ischemic myocardial injuries of rats. Phytother Res 2008 J;22(7):985-989. doi:10.1002/ptr.2452
27. Zhu M, Xie J. LncRNA MALAT1 Promotes Ulcerative Colitis by Upregulating lncRNA ANRIL. Dig Dis Sci 2020 J;65(11):3191-3196. doi:10.1007/s10620-020-06093-w
28. Yang W, Li X, Qi S, Li X, Zhou K, Qing S, Zhang Y, Gao MQ. lncRNA H19 is involved in TGF-β1-induced epithelial to mesenchymal transition in bovine epithelial cells through PI3K/AKT Signaling Pathway. PeerJ 2017 J;5:e3950. doi:10.7717/peerj.3950
29. Lei N, Kong P, Chen S, Wang Q, Tang X, Liu F. Upregulated NORAD is implicated in apoptosis, inflammation, and oxidative stress in ulcerative colitis through the nuclear factor-κappaB signaling. Eur J Gastroenterol Hepatol 2022 J;34(6):630-639. doi:10.1097/MEG.0000000000002370
30. Zhang M, Bai X, Zeng X, Liu J, Liu F, Zhang Z. circRNA-miRNA-mRNA in breast cancer. Clin Chim Acta 2021 J;523:120-130. doi:10.1016/j.cca.2021.09.013
31. Chang X, Zhu G, Cai Z, Wang Y, Lian R, Tang X, Ma C, Fu S. miRNA, lncRNA and circRNA: Targeted Molecules Full of Therapeutic Prospects in the Development of Diabetic Retinopathy. Front Endocrinol (Lausanne) 2021 J;12:771552. doi:10.3389/fendo.2021.771552
32. Zhou J, Liu J, Gao Y, Shen L, Li S, Chen S. miRNA-Based Potential Biomarkers and New Molecular Insights in Ulcerative Colitis. Front Pharmacol 2021 J;12:707776. doi:10.3389/fphar.2021.707776
33. Pierdomenico M, Cesi V, Cucchiara S, Vitali R, Prete E, Costanzo M, Aloi M, Oliva S, Stronati L. NOD2 Is Regulated By Mir-320 in Physiological Conditions but this Control Is Altered in Inflamed Tissues of Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis 2016 J;22(2):315-326. doi:10.1097/MIB.0000000000000659
34. Singh UP, Murphy AE, Enos RT, Shamran HA, Singh NP, Guan H, Hegde VL, Fan D, Price RL, Taub DD, Mishra MK, Nagarkatti M, Nagarkatti PS. miR-155 deficiency protects mice from experimental colitis by reducing T helper type 1/type 17 responses. Immunology 2014 J;143(3):478-489. doi:10.1111/imm.12328
35. Jin X, Chen D, Zheng RH, Zhang H, Chen YP, Xiang Z. miRNA-133a-UCP2 pathway regulates inflammatory bowel disease progress by influencing inflammation, oxidative stress and energy metabolism. World J Gastroenterol 2017 J;23(1):76-86. doi:10.3748/wjg.v23.i1.76
36. Yen CY, Huang CY, Hou MF, Yang YH, Chang CH, Huang HW, Chen CH, Chang HW. Evaluating the performance of fibronectin 1 (FN1), integrin α4β1 (ITGA4), syndecan-2 (SDC2), and glycoprotein CD44 as the potential biomarkers of oral squamous cell carcinoma (OSCC). Biomarkers 2013 J;18(1):63-72. doi:10.3109/1354750X.2012.737025
37. Cadoff EB, Sheffer R, Wientroub S, Ovadia D, Meiner V, Schwarzbauer JE. Mechanistic insights into the cellular effects of a novel FN1 variant associated with a spondylometaphyseal dysplasia. Clin Genet 2018 J;94(5):429-437. doi:10.1111/cge.13424
38. Su H, Xie J, Wen L, Wang S, Chen S, Li J, Qi C, Zhang Q, He X, Zheng L, Wang L. LncRNA Gas5 regulates Fn1 deposition via Creb5 in renal fibrosis. Epigenomics 2021 J;13(9):699-713. doi:10.2217/epi-2020-0449