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HucMSC-Ex alleviates inflammatory bowel disease via the lnc78583-mediated miR3202/HOXB13 pathway

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As a group of nonspecific inflammatory diseases affecting the intestine, inflammatory bowel disease (IBD) exhibits the characteristics of chronic recurring inflammation, and was proven to be increasing in incidence (Kaplan, 2015). IBD induced by genetic background, environmental changes, immune functions, microbial composition, and toxin exposures (Sasson et al., 2021) primarily includes ulcerative colitis (UC) and Crohn's disease (CD) with complicated clinical symptoms featured by abdominal pain, diarrhea, and even blood in stools (Fan et al., 2021; Huang et al., 2021). UC is mainly limited to the rectum and the colon, while CD usually impacts the terminal ileum and colon in a discontinuous manner (Ordás et al., 2012; Panés and Rimola, 2017). In recent years, many studies have suggested the lack of effective measures in the diagnosis and treatment of IBD, prompting an urgent need for new strategies to understand the mechanisms of and offer promising therapies for IBD.

Although traditional approaches have focused on protein-coding RNAs (messenger RNAs (mRNAs)), the existing evidence is highly suggestive that non-coding RNAs, mainly including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs

(circRNAs), and ribosomal RNAs (rRNAs), have potential functions in IBD (Esteller, 2011). Initially considered as “dark matter” and the transcriptional noise of genes, lncRNAs are a class of transcript RNA that are more than 200 nucleotides in length without protein-coding capacity (Jathar et al., 2017). As lncRNAs are involved in chromatin modification, gene transcriptional regulation, protein post-translational regulation, and miRNA regulation (Qian et al., 2019), with the increasing development of high-throughput sequencing, there is now emerging evidence that sheds light on the importance of lncRNAs. LncRNAs exhibit specific expression in different cells, tissues, and organs, thereby affecting cell proliferation, differentiation, apoptosis, and migration. Previous studies have indicated the marked roles of lncRNAs in cancers, inflammation, and other diseases. For example, one of the most often investigated lncRNAs, H19 participates in the onset and progression of lung cancer (Huang et al., 2018), ovarian cancer (Barnhoorn et al., 2018), gastric cancer (Gan et al., 2019), and Parkinson's disease (Jiang et al., 2020) through different pathways. A recent study also elucidated that lncRNA small nucleolar RNA host gene 6 (SNHG6) can promote hepatocellular carcinoma progression by interacting with heterogeneous nuclear ribonucleoprotein L/polypyrimidine tract-binding protein 1 (HNRNPL/PTBP1) to facilitate SET domain containing 7/leucine zipper transcription factor-like 1 (SETD7/LZTFL1) mRNA destabilization (Wang et al., 2021). Moreover, further studies have provided insights into the association between lncRNAs and exosomes. Liu et al. (2021)

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found that exosomes in the pericardial fluid carry linc00636 to promote cardiac fibrosis in patients with atrial fibrillation through the miRNA-450a-2-3p/mitogen-activated protein kinase (miR-450a-2-3p/MAPK) signaling pathway.

Concerning IBD, there is also an increasing recognition of the significance of lncRNAs. For instance, the lncRNA DQ786243 was found to be overexpressed in CD patients positively linked to cyclic adenosine monophosphate (cAMP)-response element-binding protein (CREB) and forkhead transcription factor protein P3 (Foxp3) (Qiao et al., 2013). BC012900 and interferon γ -antisense RNA1 (IFNG-AS1) were proposed to be key enhancers of UC (Padua et al., 2016; Wu et al., 2016). Besides, lncRNA growth arrest-specific transcript 5 (GAS5) was indicated to be beneficial for pediatric IBD therapy via reducing the expression of matrix metalloproteinase 2 (MMP2) and MMP9 (Lucafò et al., 2019). In addition, lncRNAs have been shown to be involved in the regulation of intestinal epithelial cells, thereby improving inflammation and the functional regulation of regulatory T cells (Yarani et al., 2018). The inhibition of lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) suppresses the inflammatory response in IBD by modulating the intestinal epithelial barrier and through the exosome-mediated polarization of macrophages (Liu et al., 2018). This indicates the negative effects of NEAT1, as it enhances inflammation and disrupts the intestinal epithelial barrier function. Furthermore, lncRNA NEAT1 was proven to regulate IBD in various ways involving an exosome-mediated pathway (Jia et al., 2018).

In our study, high-throughput sequencing was applied to determine the different expression levels of lncRNAs between two pairs of colon tissues from IBD patients and their matched health controls (HCs). The lncRNA sequencing information analysis process mainly included the quality control of sequencing data, data comparison analysis, quantification of expression, identification of novel lncRNAs, analysis of differential expression, feature analysis, and target prediction of novel lncRNAs. The raw data have been uploaded to the National Center for Biotechnology Information (NCBI) platform (SUB10893884). A total of 1344 IBD-related RNAs were detected, as presented in the heatmaps (Figs. 1a and 1b) and Jensen-Shannon (JS) score (Fig. 1c), among which 618 were lncRNAs and

726 were mRNAs. The JS scores showed a positive relationship with tissue specificity. After excluding lncRNAs with a $|\log_2 \text{Ratio}|$ lower than 1 and a P -value greater than 0.05, we identified 72 differentially expressed lncRNAs including 31 known lncRNAs and 41 novel lncRNAs named after MSTRG, as well as 325 differentially expressed mRNAs (Figs. 1d–1f). Among these RNAs, 18 known lncRNAs, 15 novel lncRNAs, and 251 mRNAs were upregulated, while 13 known lncRNAs, 26 novel lncRNAs, and 74 mRNAs were downregulated (Fig. 1g). Herein, we focused on the novel lncRNAs that have been classified into long intergenic non-coding RNAs (lincRNAs) (49%), intronic lncRNAs (34%), and antisense lncRNAs (17%) according to their locations (Fig. 1h).

Next, we verified the novel lncRNAs by quantitative real time-polymerase chain reaction (qRT-PCR) in human colorectal mucosa cells (fetal human cells (FHCs)) and found that eight lncRNAs were consistent with the findings of RNA sequencing (RNA-seq), which included five upregulated MSTRG genes (117344, 153448, 83406, 151143, and 182523), as well as three downregulated MSTRG genes (24161, 78583, and 185073). The results are presented in Figs. 2a and 2b.

Given the outcome of the cell experiments, we further tested the expression levels of these lncRNAs by collecting more human tissues. The results of qRT-PCR showed that the MSTRG.78583 was significantly decreased in IBD patients (Fig. 2c). Because the high-throughput sequencing results detected one of the targeted mRNAs of MSTRG.78583, homeobox B13 (HOXB13), which showed significantly decreased expression, we also tested HOXB13 expression in IBD patients. Both qRT-PCR and immunohistochemistry (IHC) provided the same results that the mRNA and protein levels of HOXB13 were significantly reduced in IBD (Figs. 2d–2f). Under this circumstance, we chose MSTRG.78583 as our target for further studies and renamed it as lnc78583.

In order to explore the effect of lnc78583 on lipopolysaccharide (LPS)-induced colorectal cell inflammation, we performed the next stage of the experiment using FHC. Firstly, we found that lnc78583 was decreased after a low concentration of under 500 ng/mL LPS treatment, and showed a dependence on concentration (Fig. 3a). Based on the results, we selected 100 ng/mL as our key concentration and determined

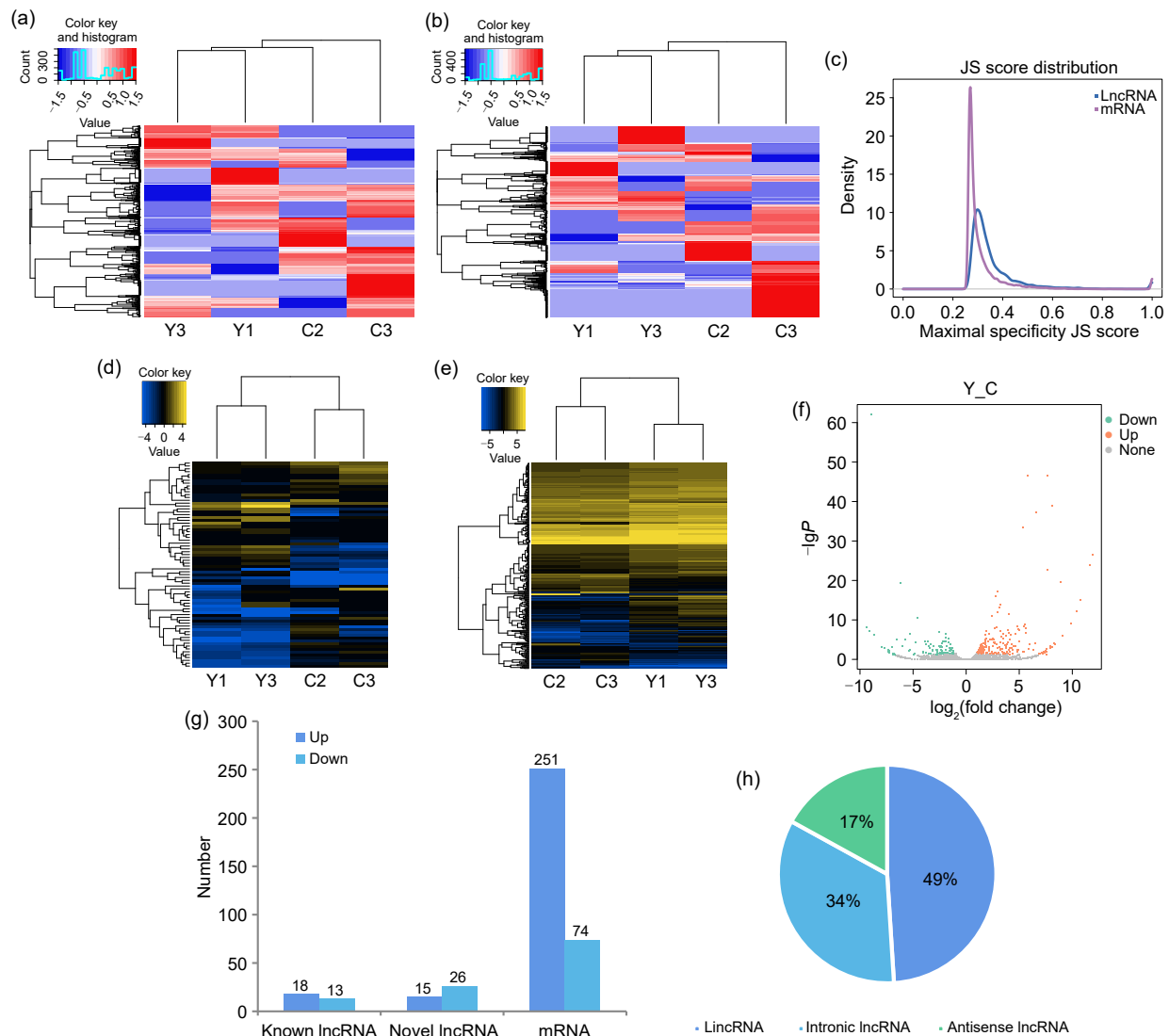


Fig. 1 Differentially expressed lncRNAs and mRNAs in IBD versus healthy control tissues. (a, b) Heatmaps depict the total lncRNAs and mRNAs determined in the colon of IBD and HCs. Red represents upregulated genes and blue represents downregulated genes. (c) The distribution image of JS score density illustrates the tissue specificity of lncRNAs and mRNAs. (d, e) Heatmaps depict the differentially expressed lncRNAs and mRNAs in IBD patients and HCs with a difference greater than 2-fold. Yellow represents high expression and blue represents low expression. (f) The volcano plot was constructed with fold-change values and P -values. Red represents upregulated genes, green represents downregulated genes, and gray represents unchanged genes. (g) The histogram indicates the numbers of differentially expressed known lncRNAs, novel lncRNAs, and mRNAs. (h) The pie chart depicts the percentages of the different types of novel lncRNAs (lincRNA, intronic lncRNA, and antisense lncRNA) identified. lncRNAs: long non-coding RNAs; mRNAs: messenger RNAs; IBD: inflammatory bowel disease; HCs: health controls; JS: Jensen-Shannon; lincRNAs: long intergenic non-coding RNAs.

the expression levels of mRNAs of inflammatory factors in addition to lnc78583 and HOXB13. The qTR-PCR analysis indicated that lnc78583 and HOXB13 were significantly decreased in the LPS group (Figs. 3b and 3c). Moreover, the pro-inflammatory factors, tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) were highly expressed, while an anti-inflammatory factor, IL-10, was lowly expressed in the LPS group

(Figs. 3d–3f). Altogether, these data demonstrated that lnc78583 and HOXB13 had a negative relationship with inflammation of FHC. Furthermore, we successfully overexpressed lnc78583 in FHC (Fig. 3g). The qRT-PCR analysis showed that the overexpression of lnc78583 upregulated HOXB13 and IL-10 to inhibit inflammation (Figs. 3h and 3i). Western blot analysis confirmed the increased expression of HOXB13,

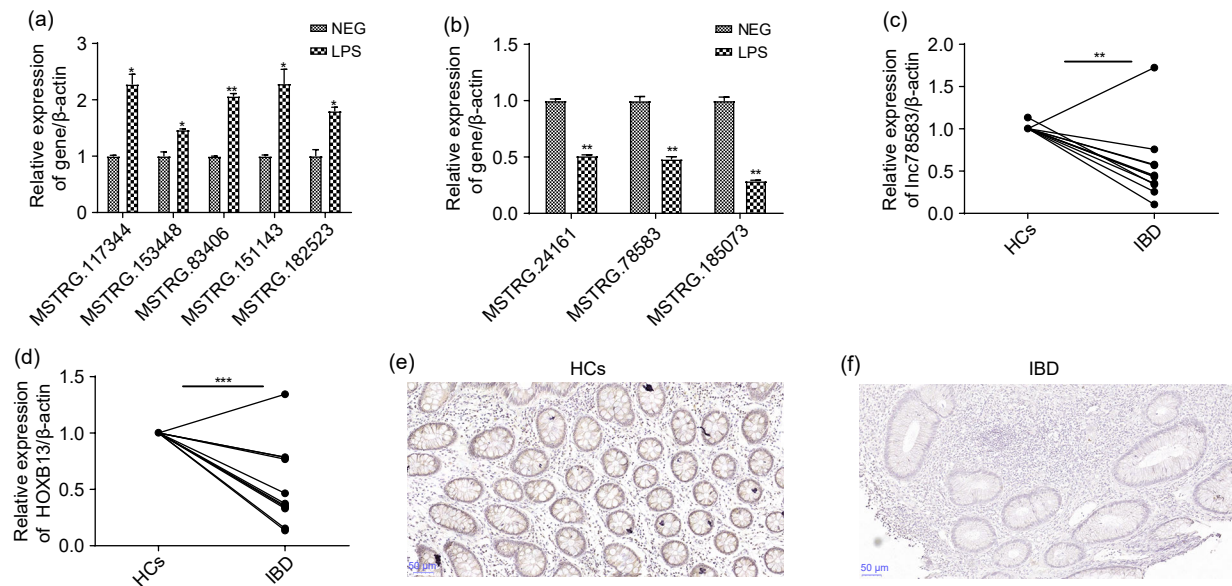


Fig. 2 Verification of novel lncRNAs. (a, b) The qRT-PCR analysis of novel lncRNAs after treatment with or without LPS in FHC. Data are expressed as mean±standard error of the mean (SEM), $n=11$. * $P<0.05$, ** $P<0.01$ vs. negative group (NEG). (c, d) The qRT-PCR analysis of lnc78583 and HOXB13 in HC and IBD patients ($n=11$). ** $P<0.01$, *** $P<0.001$. (e, f) IHC analysis of HOXB13 protein in HCs (e) and IBD (f). lncRNAs: long non-coding RNAs; qRT-PCR: quantitative real time-polymerase chain reaction; LPS: lipopolysaccharide; FHC: fetal human cell; HOXB13: homeobox B13; HC: health control; IBD: inflammatory bowel disease; IHC: immunohistochemistry.

whereas the activation of nuclear factor- κ B (NF- κ B), which mainly mediates inflammation, was also partially inhibited (Fig. 3j). We used an image processing software, ImageJ, to clearly present our results (Figs. 3k and 3l). In addition, the cell counting kit-8 (CCK8) assay indicated enhanced cell viability through the overexpression of lnc78583, which again contributed to a reduced lactic dehydrogenase (LDH) release (Figs. 3m and 3n). In conclusion, lnc78583 exerted a protective effect on LPS-induced FHC inflammation through targeting HOXB13.

Given that many previous studies have revealed the damage-repairing roles of human umbilical cord mesenchymal stem cells-derived exosome (hucMSC-Ex) in many diseases including IBD, in the present study, we explored whether hucMSC-Ex regulates lnc78583 during IBD mitigation. Firstly, we examined hucMSC-Ex by nanoparticle tracking analysis (NTA) and western blot, which showed a peak exosome diameter of about 167.2 nm with the positive expression of cluster of differentiation 9 (CD9), CD63, and heat shock protein 70 (HSP70) (Figs. 4a and 4b). In addition, an electron microscope was used to observe and confirm the exosomes (Fig. 4c). As predicted, the cell viability of FHC was improved in the hucMSC-Ex+LPS group compared with the LPS-untreated group

as analyzed through the CCK8 kit (Fig. 4d). Meanwhile, the LDH released in the hucMSC-Ex was significantly reduced (Fig. 4e). Furthermore, a qRT-PCR assay was conducted, which showed that hucMSC-Ex elevated the expression levels of lnc78583, HOXB13, and IL-10, as compared with LPS stimulation (Figs. 4f–4h). In addition to mRNA levels, the western blot analysis indicated that the protein level of HOXB13 was increased in the hucMSC-Ex+LPS group with a decreasing activated expression level of phosphorylated NF- κ B (p-NF- κ B) (Fig. 4i). We also used ImageJ to clearly represent our results (Figs. 4j and 4k). Altogether, these observations provide evidence that hucMSC-Ex alleviates LPS-induced FHC inflammation by regulating the lnc78583/HOXB13 axis.

Since multiple studies have evidenced the lncRNA-miRNA-mRNA relationship network, we explored the miRNA that possibly engages lnc78583 and HOXB13. We first predicted their target genes in the miRDB database (<http://mirdb.org>) and found that the miRNA miR3202 had binding sites with lnc78583 and HOXB13 as depicted in Fig. 5a. Subsequently, we estimated the expression level of miR3202 in FHC by qRT-PCR, and found that miR3202 was upregulated after LPS stimulation, indicating a negative relation

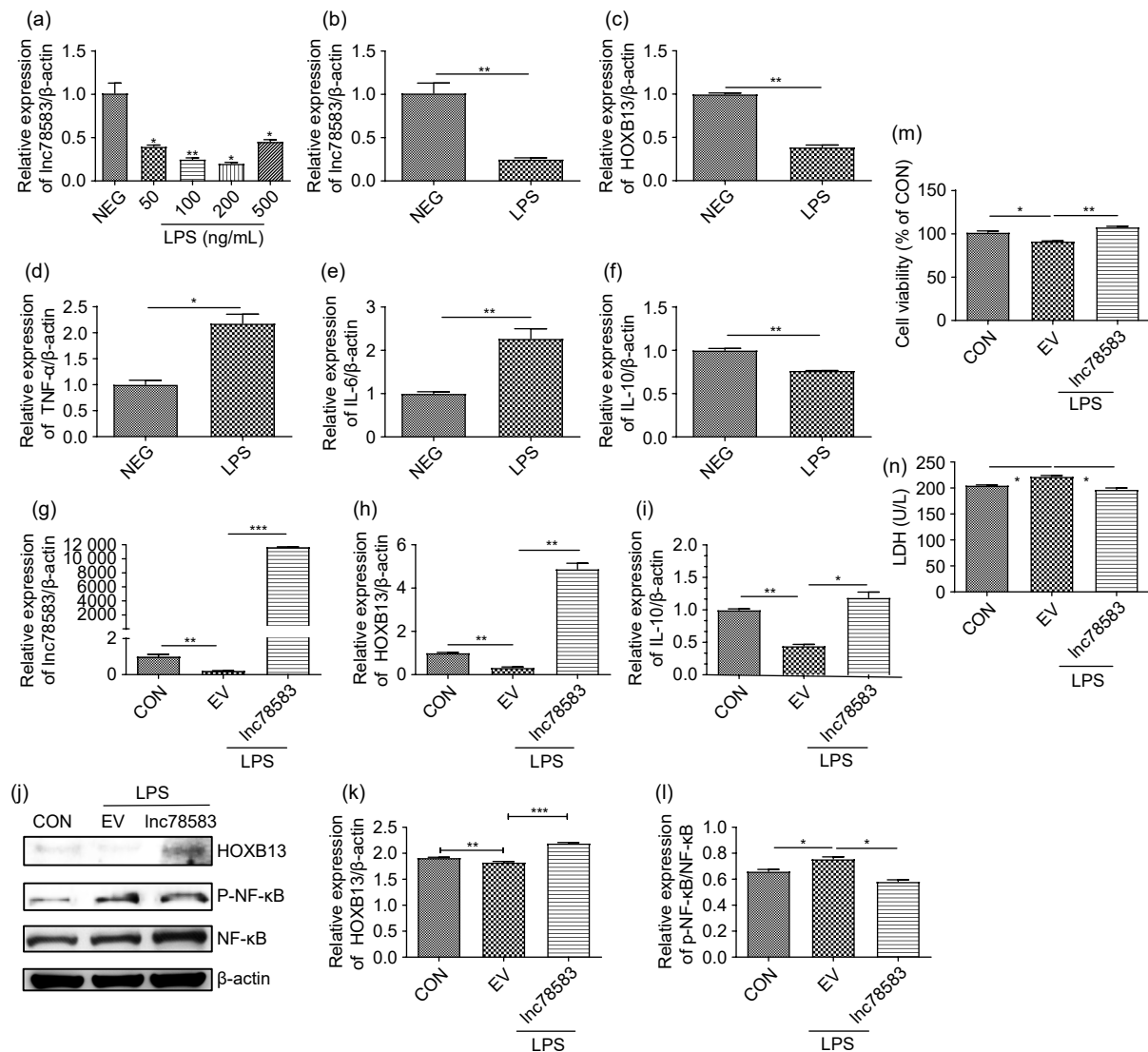


Fig. 3 Protective effect of lnc78583 on LPS-induced FHC inflammation through targeting HOXB13. (a) The qRT-PCR analysis depicts the expression of lnc78583 after treatment with LPS at different concentrations. (b–f) The qRT-PCR analyses of lnc78583 as well as HOXB13, TNF- α , IL-6, and IL-10 mRNA expression levels after treatment with or without LPS in FHC. (g) The qRT-PCR analysis indicates that lnc78583-overexpressing vector is successfully transfected into FHC after LPS treatment. (h, i) The qRT-PCR analyses of HOXB13 and IL-10 mRNA expression levels after overexpressing lnc78583 or not. (j) The protein expression levels of HOXB13, p-NF- κ B, and NF- κ B after overexpressing lnc78583 or not by western blot. (k, l) The gray values of HOXB13 and p-NF- κ B protein expression related to NF- κ B after overexpressing lnc78583 or not were analyzed by ImageJ software. (m) The CCK8 analysis illustrates the cell viability of FHC after overexpressing lnc78583 or not. (n) LDH release of FHC after overexpressing lnc78583 or not. Group CON stands for overexpressing EV but without LPS treatment, group EV stands for overexpressing EV after LPS treatment, and group lnc78583 stands for overexpressing lnc78583-overexpressing vector after LPS treatment. Data are expressed as mean $\pm$ standard error of the mean (SEM), $n=11$. * $P<0.05$, ** $P<0.01$, *** $P<0.001$. LPS: lipopolysaccharide; FHC: fetal human cell; HOXB13: homeobox B13; qRT-PCR: quantitative real time-polymerase chain reaction; TNF- α : tumor necrosis factor- α ; IL: interleukin; mRNA: messenger RNA; p-NF- κ B: phosphorylated nuclear factor- κ B; CCK8: cell counting kit-8; LDH: lactic dehydrogenase; EV: empty vector; NEG: negative group.

with lnc78583 and HOXB13 in FHC (Fig. 5b). Next, we transfected FHC with lnc78583 (Fig. 5c) and the results indicated that the overexpression of lnc78583 significantly inhibited miR3202 expression (Fig. 5d).

Then, to verify the relation of miR3202 with HOXB13, we transfected FHC with miR3202 mimics and miR3202 inhibitor (Fig. 5e), and found HOXB13 to be significantly decreased in the miR3202 mimics

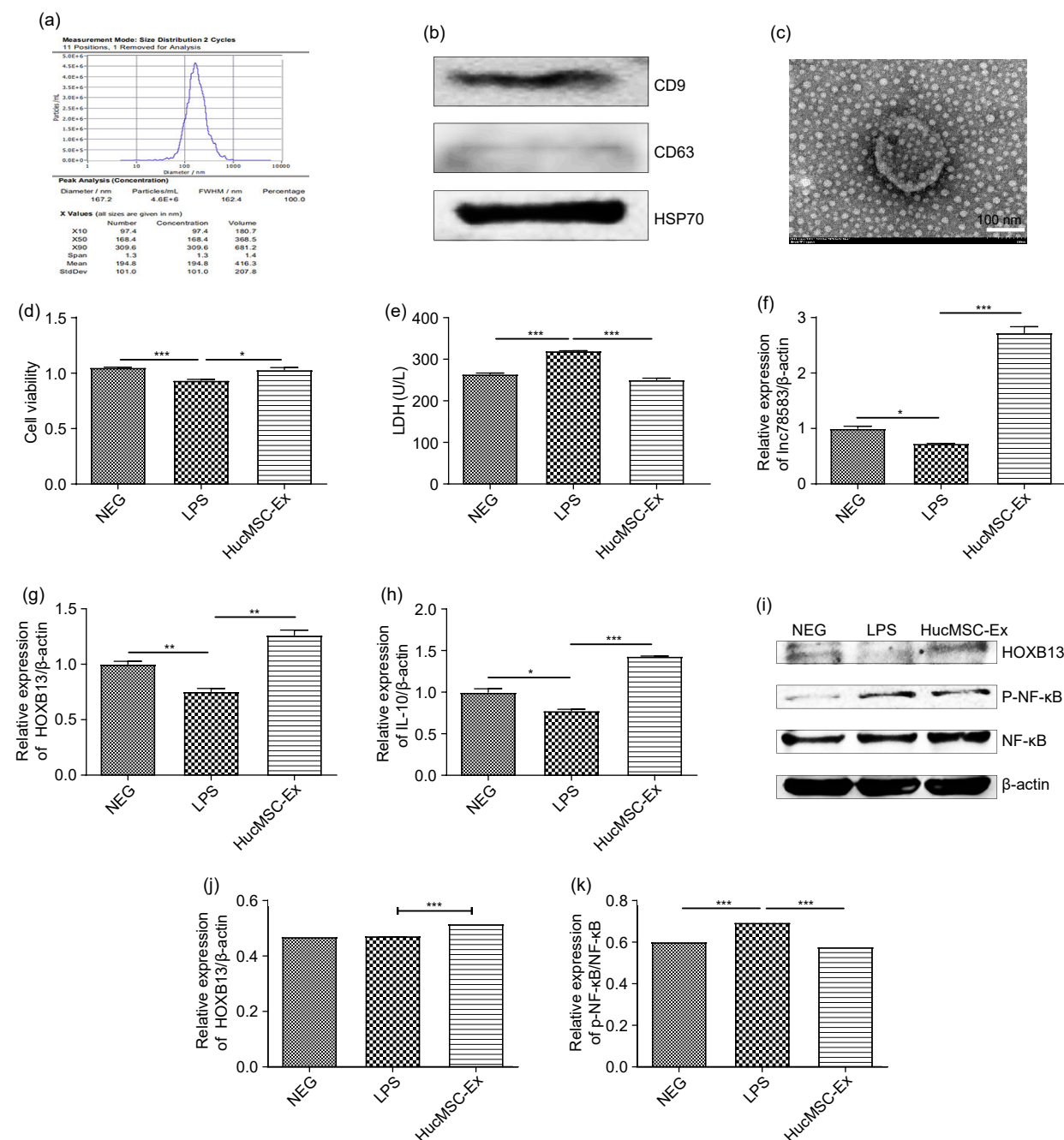


Fig. 4 Alleviation effect of hucMSC-Ex against LPS-induced FHC inflammation through lnc78583/HOXB13. (a) NTA analysis of hucMSC-Ex diameter. (b) Surface markers CD9, CD63, and HSP70 of hucMSC-Ex shown by western blot. (c) Electron microscope image of hucMSC-Ex. (d) CCK8 analysis illustrating the cell viability of FHC after treatment with or without hucMSC-Ex. (e) LDH release of FHC after treatment with or without hucMSC-Ex. (f–h) qRT-PCR analyses of lnc78583, HOXB13, and IL-10 mRNA expression levels after treatment with or without hucMSC-Ex. (i) The protein expression levels of HOXB13, p-NF-κB, and NF-κB after treatment with or without hucMSC-Ex. (j, k) The gray values of HOXB13 and p-NF-κB protein expression related to NF-κB after treatment with or without hucMSC-Ex were analyzed by ImageJ software. Data are expressed as mean±standard error of the mean (SEM), $n=11$. * $P<0.05$, ** $P<0.01$, *** $P<0.001$. HucMSC-Ex: human umbilical cord mesenchymal stem cells-derived exosome; LPS: lipopolysaccharide; FHC: fetal human cell; HOXB13: homeobox B13; NTA: nanoparticle tracking analysis; CD: cluster of differentiation; HSP70: heat shock protein 70; CCK8: cell counting kit-8; LDH: lactic dehydrogenase; qRT-PCR: quantitative real time-polymerase chain reaction; IL-10: interleukin-10; mRNA: messenger RNA; p-NF-κB: phosphorylated nuclear factor-κB; NEG: negative group.

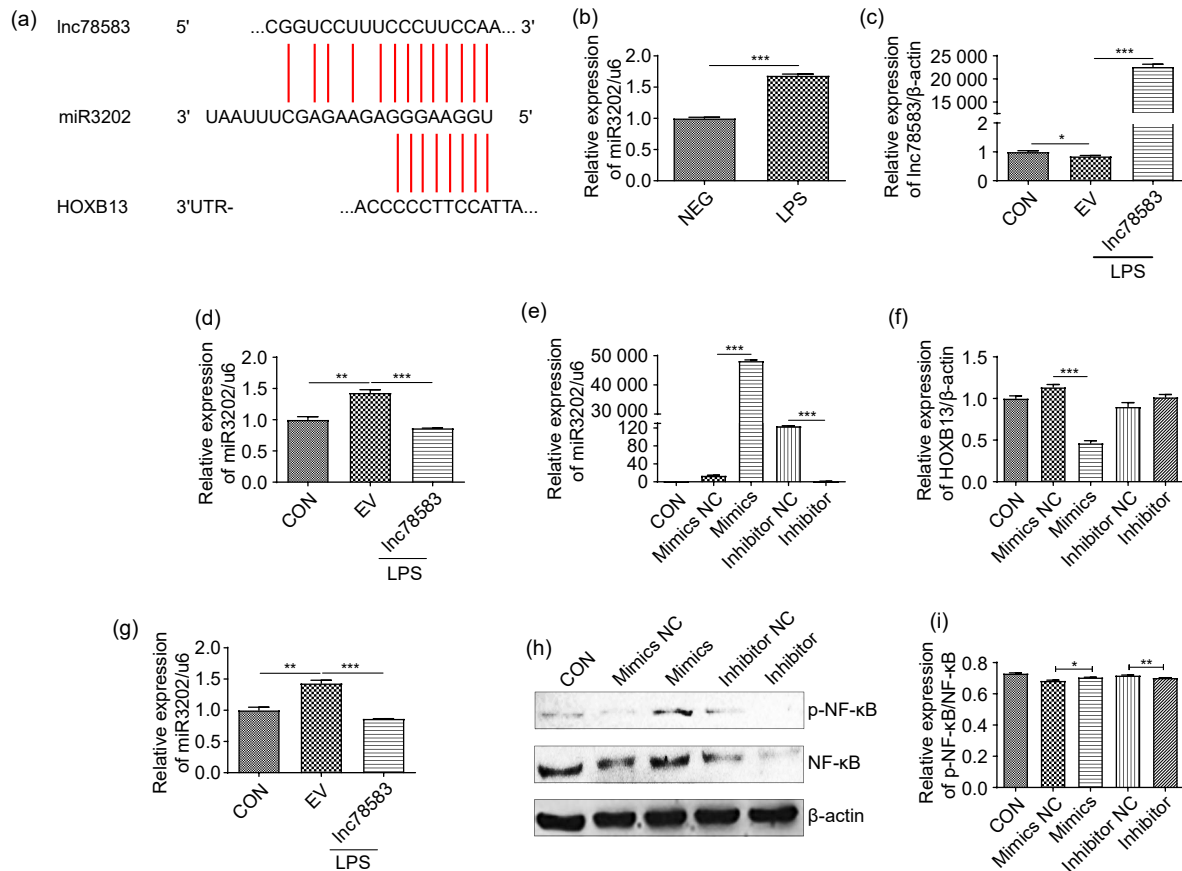


Fig. 5 miR3202 functioned as a sponge for lnc78583 and HOXB13. (a) The binding sites of miR3202 with lnc78583 and HOXB13. (b) qRT-PCR analysis of miR3202 after treatment with or without LPS in FHC. (c, d) qRT-PCR analyses of lnc78583 and miR3202 after overexpressing lnc78583 or not. (e) The qRT-PCR analysis indicates that miR3202 mimics and inhibitors were successfully transfected into FHC. (f) The qRT-PCR analysis indicates that HOXB13 is downregulated after transfecting with miR3202 mimics. (g) miR3202 expression level after treatment with hucMSC-Ex by qRT-PCR. (h) The protein expression levels of p-NF-κB and NF-κB by western blot after transfecting with miR3202 mimics and inhibitor. (i) The gray value of p-NF-κB protein expression related to NF-κB after transfecting with miR3202 mimics and inhibitor was analyzed by ImageJ software. Group CON stands for transfecting with EV but without LPS treatment, group EV stands for transfecting with EV after LPS treatment, and group lnc78583 stands for transfecting with lnc78583-overexpressing vector after LPS treatment. Data are expressed as mean±standard error of the mean (SEM), $n=11$. * $P<0.05$, ** $P<0.01$, *** $P<0.001$. HOXB13: homeobox B13; qRT-PCR: quantitative real time-polymerase chain reaction; LPS: lipopolysaccharide; FHC: fetal human cell; hucMSC-Ex: human umbilical cord mesenchymal stem cells-derived exosome; p-NF-κB: phosphorylated nuclear factor-κB; NEG: negative group; NC: negative control.

group (Fig. 5f). Finally, we detected the expression of miR3202 in hucMSC-Ex-treated FHC and indicated a consistent outcome, as hucMSC-Ex reduced the miR3202 level under inflammation (Fig. 5g). Furthermore, the western blot analysis illustrated that miR3202 had an inverse role in activating NF-κB compared with lnc78583 (Fig. 5h). The ImageJ software was similarly applied to clearly demonstrate the results of western blot (Fig. 5i).

In conclusion, through high-throughput sequencing, we found a novel lncRNA, lnc78583, located at chromosome 17 (chr17): 48752528–48755853 near

HOXB13, and proved that hucMSC-Ex alleviates inflammation through the lnc78583-mediated miR3202/HOXB13 pathway (Fig. 6).

Materials and methods

Detailed methods are provided in the electronic supplementary materials of this paper.

Acknowledgments

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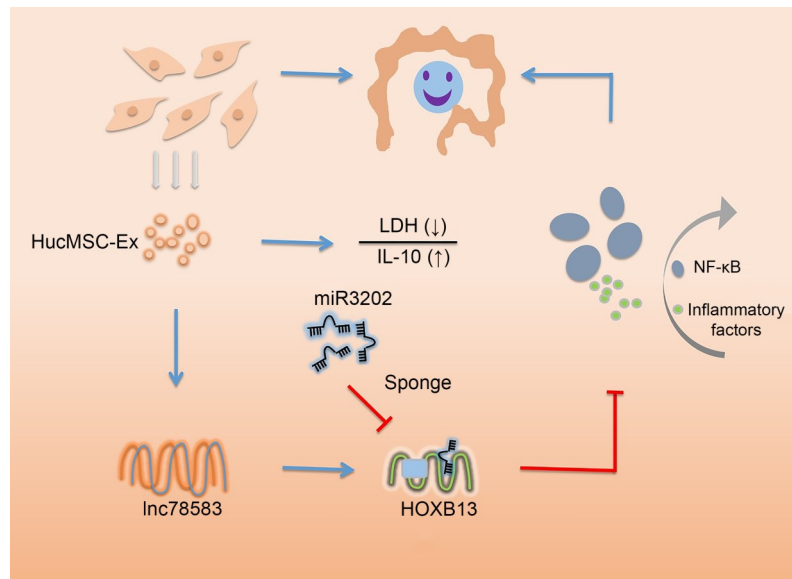


Fig. 6 Schematic diagram of the biological function and mechanism of lnc78583 during inflammation. HucMSC-Ex: human umbilical cord mesenchymal stem cells-derived exosome; LDH: lactic dehydrogenase; IL-10: interleukin-10; HOXB13: homeobox B13; NF-κB: nuclear factor-κB.

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Author contributions

Yuting XU and Li ZHANG were associated with conception and design, collection and/or assembly of data, data analysis and interpretation, and manuscript writing. Dickson Kofi Wiredu OCANSEY modified the language and edited the article. Bo WANG summarized and drew the diagram of the mechanism. Yilin HOU, Rong MEI, Yongmin YAN, and Xu ZHANG were associated with data analysis and interpretation. Zhaoyang ZHANG and Fei MAO guided the article and provided opinions. All authors have read and approved the final version of the article, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Yuting XU, Li ZHANG, Dickson Kofi Wiredu OCANSEY, Bo WANG, Yilin HOU, Rong MEI, Yongmin YAN, Xu ZHANG, Zhaoyang ZHANG, and Fei MAO declare that they have no conflict of interest.

All participants gave informed consent and this research was performed with the permission of institutions involved and approval from the Ethical Committee of Jiangsu University (No. 2014280).

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Supplementary information

Materials and methods