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Original Article

LncRNA-Anrel promotes the proliferation and migration of synovial fibroblasts through regulating miR-146a-mediated annexin A1 expression

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Abstract: Objective: Increasing evidence demonstrates that long non-coding RNAs (lncRNAs) are closely related to multiple human autoimmune diseases, and their dysregulation is tightly linked to inflammation and disease progression. Nonetheless, little is known about the consequences of aberrant expression of lncRNAs during rheumatoid arthritis (RA) development. In this study, we screened for the expressions of lncRNAs in RA synovial fibroblasts (RA-SF) and investigated their functions in RA-SF proliferation and migration, and the relevant underlying mechanisms. Methods: The lncRNAs expression profiles were interrogated with microarrays. The expressions of key lncRNAs were confirmed in synovial fibroblasts from RA patients and MH7A cells using qRT-PCR. Proliferations and migrations of MH7A and HFL-1 cells were evaluated using CCK-8 assay and cell migration assay kits, respectively. The expression of inflammatory cytokines (IL-6, IL-1β, and TNF-α) and cell migration related proteins (MMP-1 and MMP-3) were evaluated using qRT-PCR and western blotting. Collagen type II-induced arthritis (CIA) in mice was used as an animal model of RA. Results: Nine lncRNAs were significantly altered in RA-SF, of which lncRNA-000239 showing the most significant upregulation. Overexpression of lncRNA-000239 significantly enhanced the proliferation and migration of human RS-SF cells (MH7A), while the opposite effect was observed with lncRNA-000239 silencing. Importantly, lncRNA-000239 enhanced annexin A1 expression by upregulating the expression of miR-146a. Moreover, locally enhanced expression of lncRNA-000239 promoted the onset of arthritis in CIA. Conclusion: These data indicate that lncRNA-000239 upregulates annexin A1 expression via miR-146a and thus, promotes the proliferation and migration of RA-SF. This highlights a potential role of lncRNA-000239 as an inflammatory factor of RA.

Keywords: lncRNA, rheumatoid arthritis, synovial fibroblasts, annexin A1, miR-146a

Introduction

Rheumatoid arthritis (RA) is an inflammatory disease characterized by infiltrating leukocytes, monocytes, and macrophages in the joint synovial fluid and in the surrounding synovial tissue [1, 2]. Irreversible bone and joint damage can occur within two years of disease onset, even affecting other extra-articular tissues, including the skin, blood vessels, heart, lungs, and muscles [3]. The epidemiological and economic burden of RA is heavy in China [4]. This disease results in functional limitations, working disability, and poor quality of life. However, diagnostic and treatment options are still very limited. A better understanding of the pathological mechanisms of RA is critical for the identification of novel diagnostic biomarkers and therapeutic strategies [5].

Rheumatoid arthritis synovial fibroblasts (RA-SF) are involved in the initiation and perpetuation of RA, and thus distinguish RA from other inflammatory disorders of the joints. Growing evidence suggests that RA-SF activation (e.g., by responses of the innate immune system) is an early step in the development of RA [6]. Proliferation and migration of synovial fibroblasts play a significant role in the occurrence and development of RA.

Long non-coding RNAs (lncRNAs), which are over 200 nucleotides long, are a class of non-coding RNAs that are widely expressed in

eukaryotic cells. LncRNAs interact with proteins, DNA, and RNA, and therefore regulate a wide range of cell functions. Owing to their potential functions, lncRNAs have recently received extensive attention in the pathogenesis of various diseases. Early studies mostly focused on the roles of lncRNAs in genomic imprinting, cancer, and cell differentiation [7, 8]. Recently, accumulating evidences have demonstrated that lncRNAs play distinct and specialized roles in modulating immune cell differentiation and activation, suggesting that they are very important in human autoimmune diseases [9-12]. Therefore, lncRNAs have exhibited superior potential as diagnostic and prognostic biomarkers compared to protein-coding genes.

Although thousands of lncRNAs were discovered and recorded in several public databases, few lncRNAs have been functionally well annotated [13, 14]. Data on the relationship between lncRNAs and functionally related mRNAs or microRNAs (miRNAs) in humans are limited and inconsistent [15-17]. In this study, we screened for various lncRNAs in RA-SF and focused on elucidating whether and how the aberrant expressed lncRNA is associated with RA pathogenesis.

Materials and methods

Patients

Patient samples were collected in Shanghai General Hospital, from 2017 to 2018. Five patients diagnosed with RA based on the American College of Rheumatology (ACR) criteria [18] and 5 osteoarthritis (OA) patients undergoing synovial membrane excision surgery (served as controls) were recruited. All protocols involving human tissue samples were approved by the Ethics Committee of Shanghai General Hospital, and written consent was obtained from all participants.

Synovial fibroblast extraction and cell culture

Primary synovial fibroblasts were isolated from RA and OA patients. Synovial tissues were minced and treated with 2 mg/mL collagenase I (Wako, Japan) in serum-free Ham's F12K (GIBCO, USA) at 37°C for 2 h. Primary cultured synovial cells were established and maintained in Ham's F12K supplemented with 10% heat-inactivated fetal bovine serum (Thermo, USA) at 37°C in a humidified incubator with 5% CO_2. The human RA-SF cell line MH7A and the human embryonic lung fibroblast cell line HFL-1, which were purchased from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China), were cultured in Ham's F12K medium (Gibco, USA) supplemented with 10% fetal bovine serum (Thermo, USA) in a 37°C humidified incubator with 5% CO_2.

RNA extraction and quantitative reverse-transcription PCR

Total RNA was extracted from cells using TRIzol (Invitrogen, USA), and reverse transcribed into cDNA using the Reverse Transcription System Kit (Takara, China). miRNA and lncRNA transcripts were then amplified with specific primers and their expression was normalized to β-actin.

Microarray hybridization and data analysis

OneArray (Phalanx Biotech Group, Taiwan), which contains 2,635 human lncRNAs, was used in the current study. Briefly, fluorescent targets were prepared from 2.5 μg total RNA using the lncRNAULS Labeling kit (Kreatech Diagnostics, The Netherlands). Labeled lncRNAs were enriched using NanoSep 100K (Pall Corporation, USA), and enriched products were hybridized to OneArray in Phalanx hybridization buffer in the OneArray Hybridization Chamber at 37°C overnight. Nonspecific bound targets were removed with three washing steps. Following washes, the slides were dried and scanned using an Axon 4000B scanner (Molecular Devices, USA).

Plasmid construction, overexpression, and gene silencing of lncRNA-000239 and annexin A1

DNA sequences encoding lncRNA-000239 and annexin A1 were amplified using PCR and inserted into the pcDNA3.1 vector (Invitrogen, USA). Sequence-verified plasmids were then named as pcDNA-LncRNA-000239 and pcDNA-Annexin I, respectively. Short hairpin RNAs (shRNAs) for lncRNA-000239 and annexin A1, as well as scrambled shRNA, were purchased from Transheep (Transheep, China).

Transfections were performed using Lipofectamine 2000 (Invitrogen, USA) according to the manufacturer's instructions. MH7A and

Table 1. lncRNA microarray data for RA/Control synovial fibroblasts

SEQ_ID	*P*-value	FC Absolute	Regulation
RNALOC 000047	0.03	2.40	↑
RNALOC 000211	0.04	2.25	↓
RNALOC 000239	0.01	9.31	↑
RNALOC 000281	0.04	1.63	↑
RNALOC 000285	0.03	1.82	↑
RNALOC 000307	0.04	1.97	↑
RNALOC 000479	0.03	2.66	↑
RNALOC 000544	0.03	1.73	↓
RNALOC 000545	0.04	1.55	↑

HFL-1 cells were first transfected with pcDNA-LncRNA-000239 or pcDNA-Annexin I plus 10 μg mL^{-1} polybrene (Sigma, USA). After incubation for 72 h, cells were harvested for RNA and protein extraction. miR-146a mimics and miR negative control were purchased from Life Technologies (Carlsbad, CA, USA) and introduced into cells at a final concentration of 50 nM.

Cell proliferation and migration assay

Cell proliferation was assessed using the Cell Counting Kit-8 (Dojindo, Japan), according to the manufacturer's instructions. Briefly, approximately 5×10^3 MH7A and HFL-1 cells transfected either with pcDNA-LncRNA-000239 or pcDNA-Annexin I for different periods were suspended, seeded into 96-well plates, and treated with 10 μL per well Cell Counting Kit-8 solution for 4 h. After incubation, the absorbance at 450 nm was measured and cell proliferation curves were plotted. Cell migration was analyzed using cell migration assay kits (R&D Systems, USA) following the manufacturer's instructions. All experiments were performed in triplicates.

Western blot analysis

Cells were first lysed with cell lysis buffer supplemented with protease inhibitors, and then mixed with sodium dodecyl sulfate (SDS) sample loading buffer and boiled at 95°C for 5 min. Samples were then separated using SDS-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to a polyvinylidene fluoride membrane. Following blocking with 5% nonfat milk, the membrane was incubated with specific antibodies for specific proteins (Abcam, USA) or GAPDH (Abcam, USA) at 4°C overnight, and HRP-conjugated secondary antibodies for 1 h. After extensive washes with phosphate buffered saline with Tween 20 (PBST), immunostaining was visualized.

CIA induction and lncRNA-000239 knockdown

Eight- to ten-week-old male DBA/1 mice (Shanghai SLAC Laboratory Animal Co. Ltd., China) were injected intradermally with 100 μg chicken type II collagen (CII; Sigma-Aldrich, USA) emulsified in equal volumes of Freund's complete adjuvant (2 mg/mL; Mycobacterium tuberculosis) at the base of the tail to induce RA. shRNA-LncRNA-000239 and shRNA-scramble were synthesized and subcloned into the pIRES vector by Hansheng Inc. China (pIPES-shRNA-LncRNA-000239 and pIPES-shRNA-scramble, respectively). CIA-induced RA mice were injected in the joints every 48 h either with pIPES-shRNA-LncRNA-000239 or pIPES-shRNA-scramble, from day 1 to 20. Development and severity of arthritis were monitored daily since the first day following the second CII injection until the 60^{th} day. Disease severity was scored on a scale from 0 to 4 by visual inspection of the paws with the following score criteria: 0, no evidence of erythema and swelling; 1, erythema and mild swelling confined to the midfoot (tarsals) or ankle joint; 2, erythema and mild swelling extending from the ankle to the mid-foot; 3, erythema and moderate swelling extending from the ankle to the metatarsal joints; 4, erythema and severe swelling encompassing the ankle, foot, and digits.

Statistical analysis

Differences between the two groups were analyzed using two-tailed Student's t-test, and differences among three or more groups were analyzed using one-way ANOVA plus SNK test. Statistical analysis was performed using the SPSS 20.0 software package (SPSS, Inc., Chicago, IL, USA). *P*-values < 0.05 were considered to be significant: * < 0.05, ** < 0.01, *** < 0.001, **** < 0.0001.

Results

lncRNA-000239 expression is upregulated in RA-SF and MH7A cells

Firstly, the lncRNA OneArray kit was used to evaluate the expressions of 2,635 human

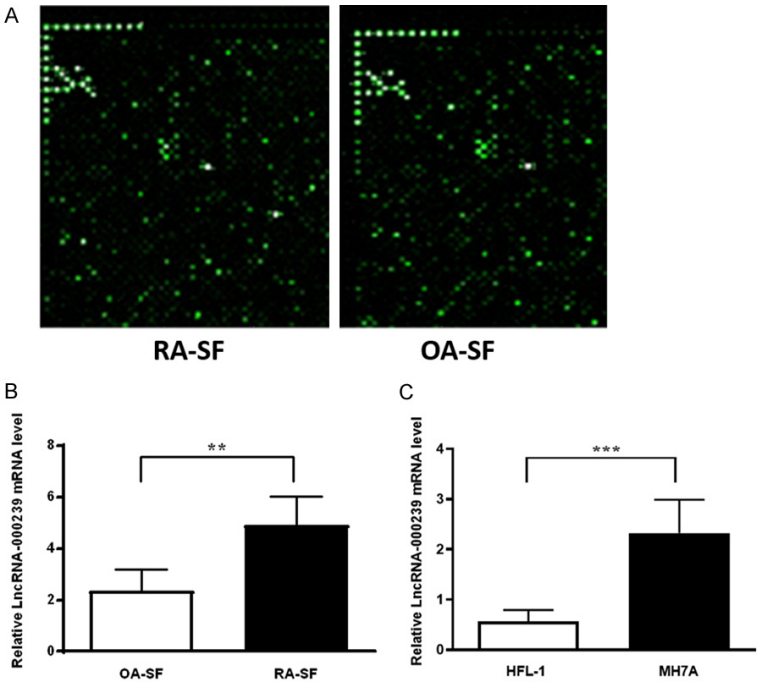

Figure 1. lncRNA-000239 expression in synovial fibroblasts. A. The expressions of 2,635 human lncRNAs in SF cells from 5 RA patients and 5 OA control individuals were measured using the lncRNA OneArray kit. B. Expression of lncRNA-000239 in RA synovial fibroblasts and control OA synovial fibroblasts (n = 5 each) was confirmed by qRT-PCR. C. Expression of lncRNA-000239 in a cultured RA synovial fibroblast cell line (MH7A) and a cultured human embryonic lung fibroblast cell line (HFL-1). Data are presented as mean ± standard error based on at least three independent experiments. **P* < 0.05, ***P* < 0.01, ****P* < 0.005.

lncRNAs in SF cells from 5 RA patients and 5 OA control individuals. Nine lncRNAs were significantly altered in RA patients (**Table 1**). lncRNA-000239 was the most significantly upregulated lncRNA compared to other lncRNAs (**Figure 1A**, P = 0.01, FC Absolute = 9.31). Using qRT-PCR, we further confirmed the upregulation of lncRNA-000239 expression in SF cells derived from RA patients and cultured human RS-SF cell lines (MH7A). Consistent with the lncRNAs OneArray results, the expressions of lncRNA-000239 were markedly upregulated in RA-SF and MH7A cells compared to OA-SF and HFL-1 cells respectively (**Figure 1B** and **1C**). Taken together, this data confirms that lncRNA-000239 expression is upregulated in RA-SF and MH7A cells.

lncRNA-000239 promotes the proliferation and migration of MH7A cells

To explore the role of lncRNA-000239 in the pathogenesis of RA, we generated MH7A and HFL-1 cells with overexpression or knockdown of lncRNA-000239. The expression level of lncRNA-000239 significantly increased in pcDNA-LncRNA-000239 transfected cells compared with the pcDNA-transfected counterparts, while MHdecreased in cells transfected with shRNA-LncRNA-000239 (**Figure 2A**). Using the cell models established above, we conducted CCK-8 cell counting assays to investigate the influence of lncRNA-000239 on MH7A and HFL-1 proliferations. Overexpression of lncRNA-000239 in MH7A cells resulted in dramatically increased cell proliferations, whereas the knockdown of lncRNA-000239 with shRNA effectively inhibited cell proliferations, suggesting that lncRNA-000239 promoted cell proliferations (**Figure 2B**). The migration assay was used to visualize the cell mobility 2 h after transfection. The migration rate of lncRNA-000239-overexpressing MH-7A cells was significantly higher than those transfected with pcDNA, whereas the migration rate of cells transfected with shRNA-LncRNA-000239 was significantly lower than those transfected with shRNA-scramble (**Figure 2C**). These results suggested that lncRNA-000239 promoted MH7A cell proliferation and migration in vitro. Overexpression or knockout of lncRNA-000239 did not change the proliferation and migration of HFL-1 cells.

lncRNA-000239 promotes MH7A proliferation by binding and upregulation of miR-146a

lncRNAs have been involved in autoimmune diseases by interacting with specific miRNAs [18]. To investigate whether the miRNAs participate in the lncRNA-000239-mediated promotion of RA-SF proliferation and migration, we predicted miRNA target sites using the online microRNA-target prediction program (http://www.mircode.org). Interestingly, we found that miR-146a has relevant binding sites to

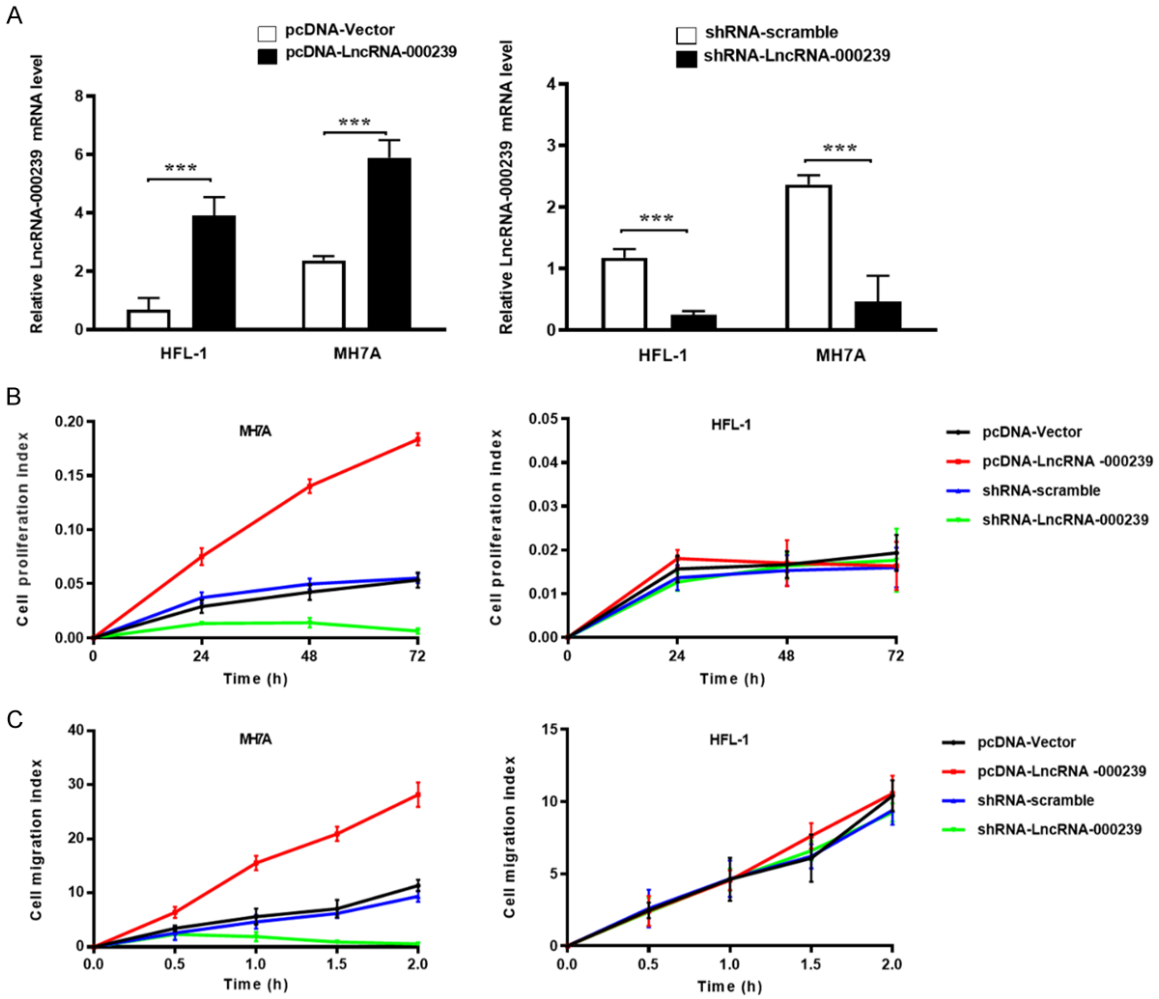

Figure 2. lncRNA-000239 promotes the proliferation and migration of MH7A cells. A. Overexpression (left) and silencing (right) of lncRNA-000239 in MH7A and HFL-1 cell lines were analyzed using qRT-PCR. B. CCK-8 assay shows the proliferation rate of MH7A (left) and HFL-1 (right) cell lines transfected with pcDNA-LncRNA-000239 or shRNA-LncRNA-000239, while the control groups were transfected with pcDNA-Vector or shRNA-scramble. C. The cell migration assay kit revealed the cell migration rate after MH7A (left) or HFL-1 (right) cells were transfected with pcDNA-LncRNA-000239 or shRNA-LncRNA-000239, while the control groups were transfected with pcDNA-Vector or shRNA-scramble. $*P < 0.05$, $**P < 0.01$, $***P < 0.005$.

lncRNA-000239 (**Figure 3A**). Then miR-146a expression levels in MH7A and HFL-1 cells with overexpression/knockdown of lncRNA-000239 were measured by qRT-PCR. The expression level of miR-146a was increased in pcDNA-LncRNA000239 transfected MH7A cells, while decreased in shRNA-LncRNA-000239 transfected MH7A cells. No difference was found in HFL-1 cells (**Figure 3B**).

To validate whether miR-146a facilitates lncRNA-000239 mediated RA progression, we ectopically expressed miR-146a in stable LncRNA-000239-overexpressing MH7A and HFL-1 cells. Interestingly, miR-146a overexpression further enhanced MH7A cell proliferation caused by lncRNA-000239 (**Figure 3C**), suggesting that lncRNA-000239 promotes RA-SF proliferation by binding and upregulation of miR-146a.

lncRNA-000239 modulates the expression of miR-146a target gene annexin A1

Annexin A1 has been recently shown to play a key role in T-cell activation and to be highly expressed in T cells from RA patients [19]. Importantly, it has been reported that miR-

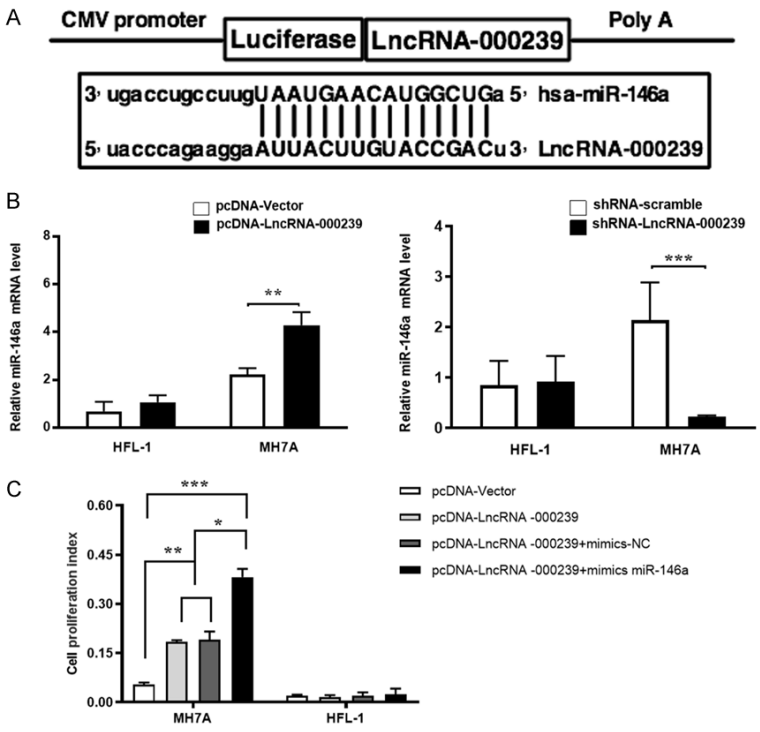

Figure 3. lncRNA-000239 promotes MH7A cell growth partly through binding of miR-146a. A. Putative binding sequence of miR-146a to lncRNA-000239 predicted by an online microRNA-target prediction software. B. Expression levels of miR-146a were measured in pcDNA-LncRNA-000239 (left) or shRNA-LncRNA-000239 (right) treated MH7A and HFL-1 cells using qRT-PCR. C. Introduction of miR-146a mimics enhanced the proliferation effect of lncRNA-000239 in MH7A cells according to the CCK-8 assay. $*P < 0.05$, $**P < 0.01$, $***P < 0.005$.

146a promotes RA by upregulating annexin A1 [20]. LncRNAs can regulate gene expression by targeting miRNAs. Given the positive correlation between miR-146a and lncRNA-000239, we speculated that lncRNA-000239 upregulates miR-146a as well as annexin A1 and thus, lncRNA-000239 promotes RA progression. To further validate this, we assessed the effects of lncRNA-000239 on annexin A1 expression by both qRT-PCR and western blot analysis. The results showed that the expression of annexin A1 was increased in MH7A cells transfected with pcDNA-LncRNA-000239 and decreased by transfection of shRNA-LncRNA-000239. No significant difference was observed in HFL-1 cells (**Figure 4A** and **4B**).

Meanwhile, both cell proliferation and migration were upregulated in MH7A cells transfected with pcDNA-Annexin A1 and decreased in cells transfected with shRNA-Annexin A1. No significant difference was observed in HFL-1 cells (**Figure 4C** and **4D**). Furthermore, we found that annexin A1 enhanced MH7A cell proliferation along with miR-146a (**Figure 4E**). Taken together, these results suggest that lncRNA-000239 promotes RA progression by modulating miR-146a/annexin A1 expression. Hence, we defined lncRNA-000239 as an Annexin Related lncRNA (lncRNA-Anrel).

Locally knockdown of lncRNA-Anrel inhibits the onset of arthritis at the joints

To determine whether lncRNA-Anrel is a driving factor for CIA development in vivo, recombinant plasmid pIRES-shRNA-LncRNA-Anrel was injected into the hind ankle of mice. Our results showed that lncRNA-Anrel knockdown significantly reduced the incidence rate and onset of CIA (**Figure 5A** and **5B**). Analysis of inflammatory cytokines and cell migration related proteins in the local joints demonstrated that the expressions of IL-6, IL-1β, and MMP-1 decreased at both the mRNA (**Figure 5C**) and protein levels (**Figure 5D**) after lncRNA-Anrel knockdown.

Discussion

Rheumatoid arthritis is an autoimmune disease with unknown etiology, occurring in approximately 1.0% of the general population. Over the past few years, considerable efforts have been made to explore the molecular mechanisms of RA. Previous studies have focused on protein-coding genes or miRNAs [19-22]. Recently, accumulated data have shown that lncRNAs participate in a variety of biological processes. Dysregulated lncRNA expression has been observed and implicated in the progression of complex diseases such as RA [9, 23]. However, the profiles and functions of lncRNAs remain largely uncharacterized, and the identification of lncRNA biomarkers in RA is a challenge.

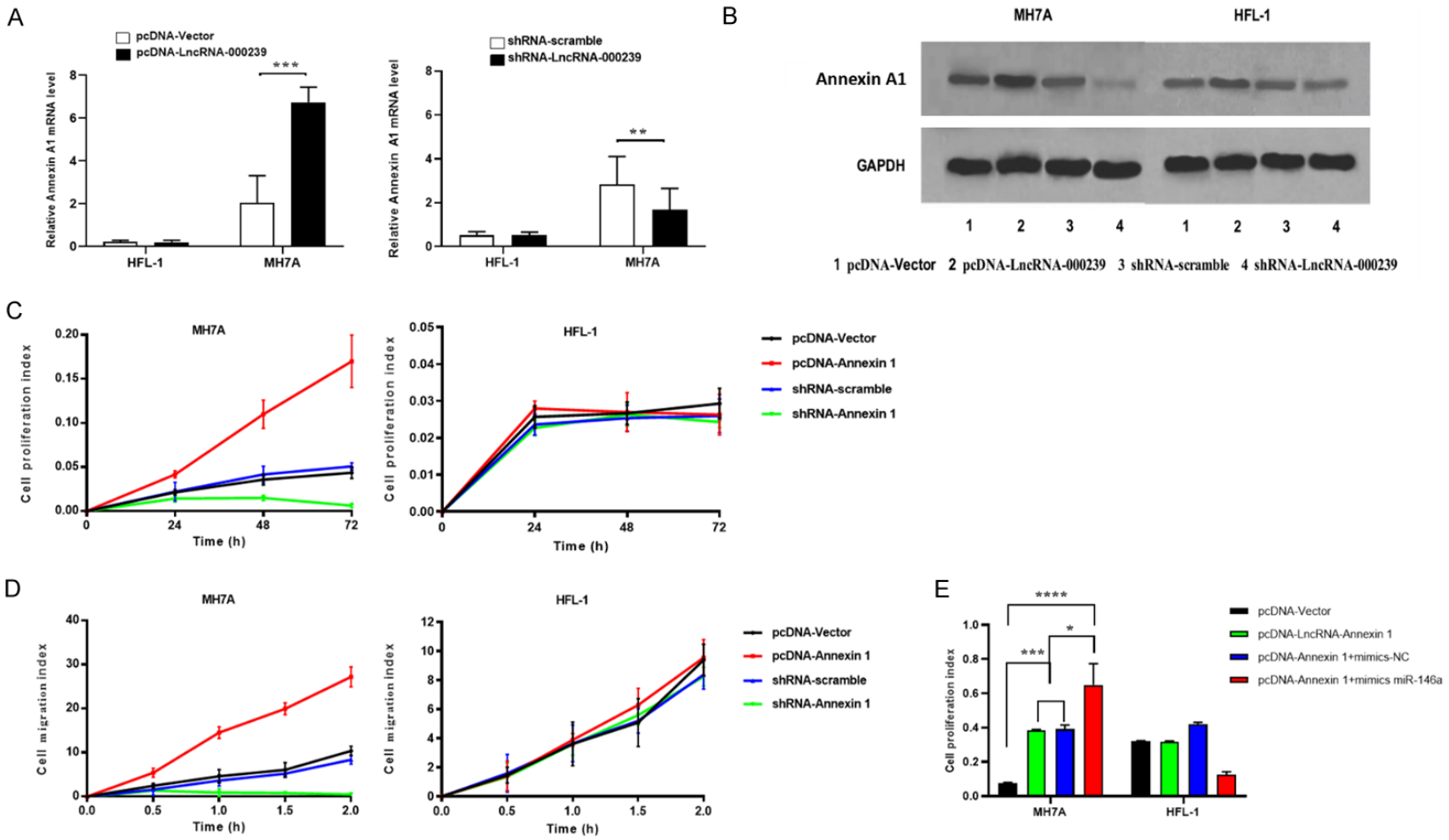

Figure 4. lncRNA-000239 modulates the expression of the endogenous miR-146a target annexin A1. A, B. After transfection with pcDNA-Vector, pcDNA/shRNA-LncRNA-000239 or shRNA-scramble, the mRNA and protein levels of annexin A1 in MH7A cells were examined using qRT-PCR and western blotting, respectively. C. The CCK-8 assay showed that the cell proliferation rate after MH7A (left) or HFL-1 (right) cells were transfected with pcDNA-Annexin I or shRNA-Annexin I, while the control groups were transfected with pcDNA-Vector or shRNA-scramble. D. Migration rate of annexin A1 overexpressing and silencing MH7A and HFL-1 cell lines as measured using the cell migration assay kits. E. After transfection with pcDNA-Annexin 1 combined with miR-46a mimics, the MH7A proliferation rate was examined using the CCK-8 kit. *$P < 0.05$, **$P < 0.01$, ***$P < 0.005$, ****$P < 0.001$.

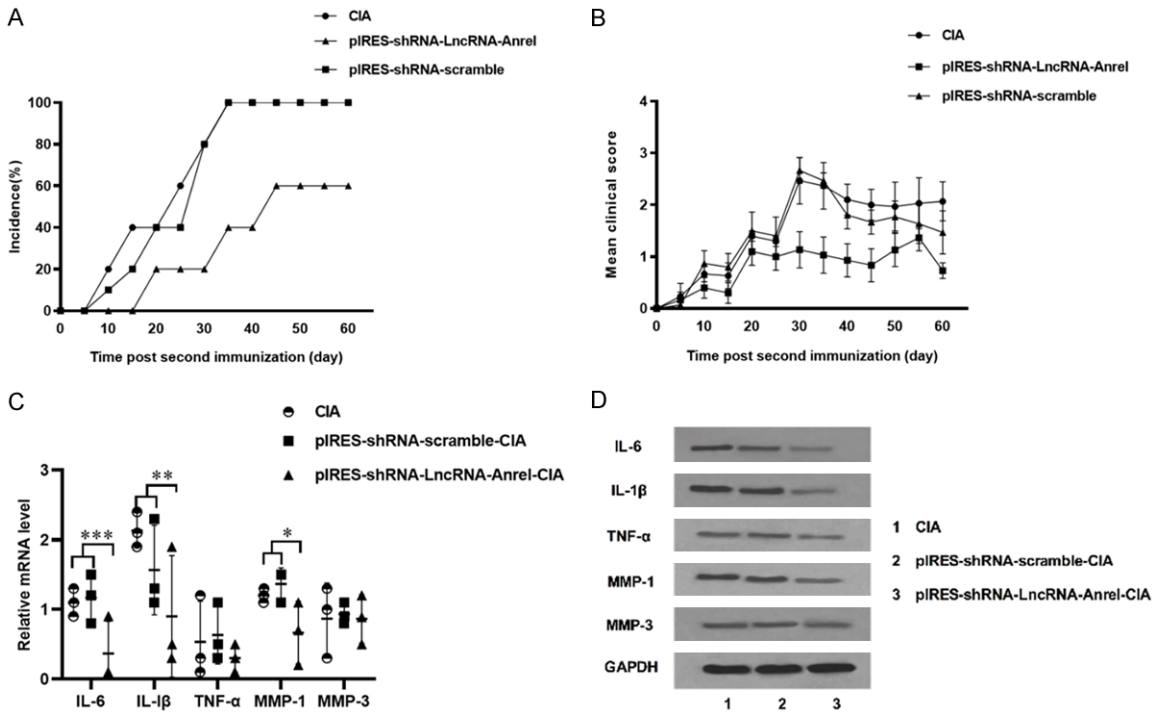

Figure 5. Effect of lncRNA-Anrel (lncRNA-000239) on the formation and development of CIA. A, B. Visual inspection of paws revealed the incidence and clinical score of collagen type II-induced arthritis in mice injected with pIRES-shRNA-LncRNA-Anrel or pIRES-shRNA-scramble, and untreated mice (n = 5 for each group). C, D. Levels of inflammatory cytokines and cell migration related proteins expression in the injury joint were detected with qRT-PCR and western blotting in each group. **P* < 0.05, ***P* < 0.01, ****P* < 0.005, *****P* < 0.001.

Hence, in our study, we first interrogated the expression profile of various lncRNAs in RA-SF and MH7A cells. We detected 9 lncRNAs, including lncRNA-Anrel, which were significantly altered in RA. lncRNA-Anrel was found to be significantly upregulated in synovial tissues of RA patients and MH7A cell lines, indicating the potential pathological and clinical implication of lncRNA-Anrel in RA. Furthermore, we also found that the overexpression of lncRNA-Anrel remarkably promoted cell proliferation and migration in vitro, while the knockdown of lncRNA-Anrel negatively regulated cell growth. Our data suggest that clinical-oriented research on lncRNA-Anrel in RA should be undertaken to further explore the role of this lncRNA in RA diagnosis and treatment.

Recently, accumulated data have shown that dysregulated lncRNA expression was observed and implicated in the progression of RA. New information about the mechanisms has suggested that lncRNAs can regulate miRNA abundance through binding based on their longer size [9, 23]. Therefore, it has been shown that an efficient way to infer the potential function of lncRNAs is by studying their relationship with miRNAs and/or mRNAs whose functions have been annotated.

In our study, we identified lncRNA-Anrel as a pro-inflammatory factor and identified a previously unknown pathway involving lncRNA-Anrel and miR-146a in RA. We found that lncRNA-Anrel was involved in a miRNA-related regulatory network of RA-SF cell growth. Mechanistic experiments demonstrated that lncRNA-Anrel promotes proliferation and migration of MH7A cells (**Figure 6**).

Consistent with our findings, a previous study verified that UCA1 was associated with miR-143 and modulated expression of the miR-143 target HK2, which provides powerful evidence that UCA1 positively regulates gene expression at the post-transcriptional level [24]. Moreover, by combining bioinformatics analysis and functional experiments in vitro and in vivo, UCA1 was found to contribute to progression of hepa-

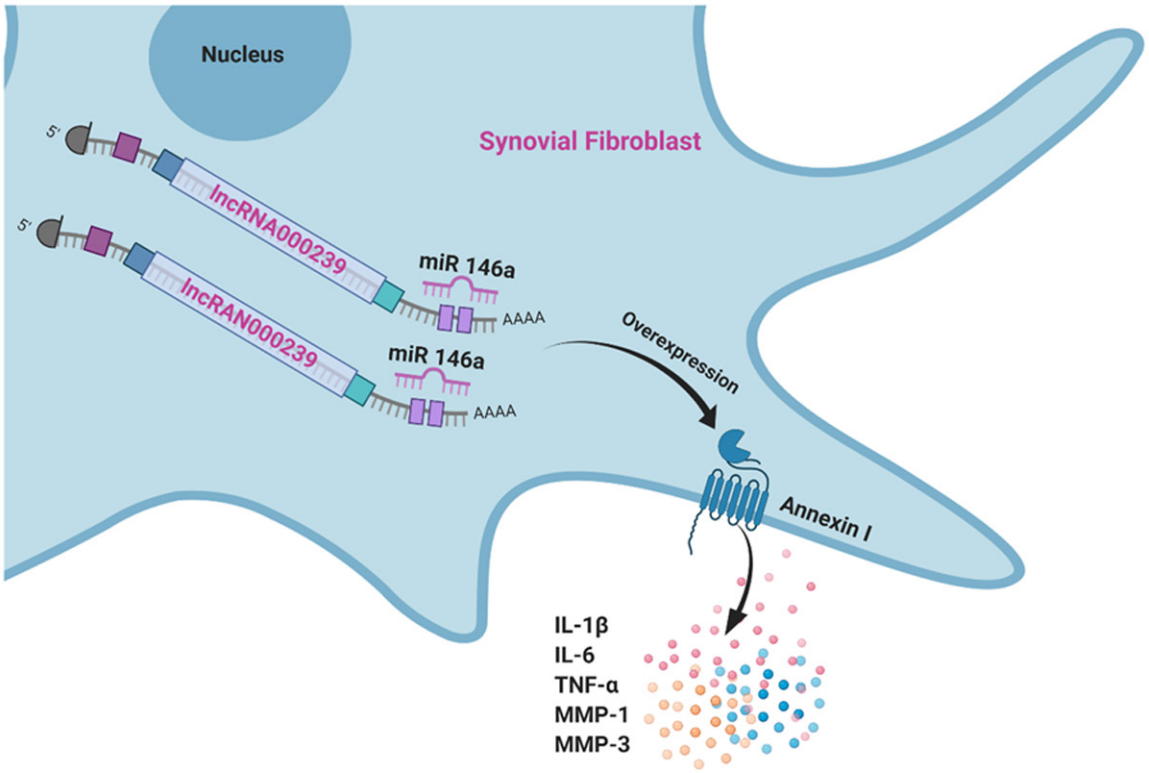

Figure 6. lncRNA-000239 upregulates annexin A1 expression via miR-146a and thus promotes the proliferation and migration of RA-SF.

tocellular carcinoma, where it acts as an endogenous sponge by directly binding to miR-216b and activating the FGFR1/ERK signaling pathway. In addition to miR-143 and miR-216b, it is interesting to investigate whether UCA1 may function by interacting with other unknown miRNAs in human tumors [25].

In summary, our studies indicate that lncRNA-Anrel expression may potentially predict the prognosis of patients with RA, and this possibility should be confirmed in future studies using large sample sizes. Our mechanistic analysis revealed the involvement of lncRNA-Anrel in promoting RA progression by interacting with miR-146a and indicated a novel lncRNA-Anrel-miR-146a-annexin A1 signaling regulatory network in RA. These findings indicate that lncRNA-Anrel is an important molecular marker for RA prognosis, an important target for RA therapy, and would add to the known crosstalk between established pathways.

Acknowledgements

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Disclosure of conflict of interest

None.

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