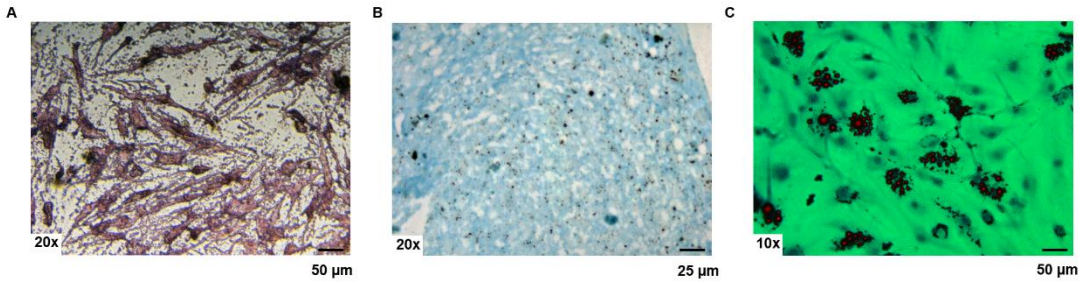
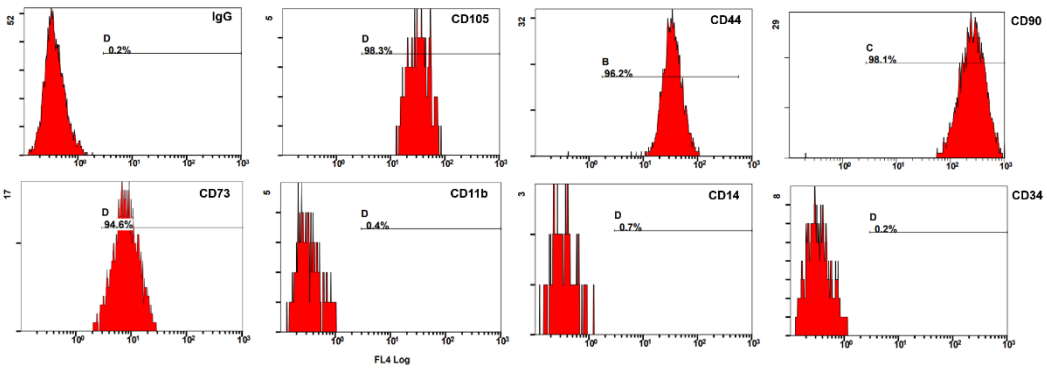
Supplementary Figure 1.



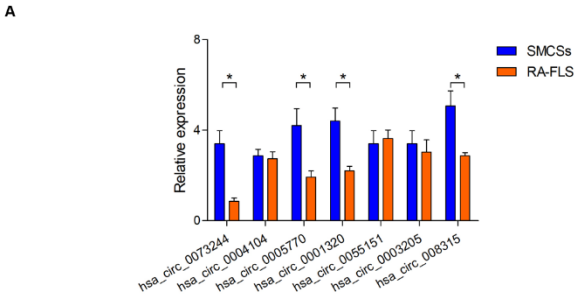
Supplementary Figure 1. Identification of SMSCs by cell differentiation.
(A) Alizarin red staining in SMSCs cultured in osteogenic differentiation medium for 21 d. (B) Alcian blue staining in SMSCs cultured in chondrogenesis differentiation medium for 21 d. (C) Oil Red O staining in SMSCs cultured in adipogenesis differentiation medium for 14 d.

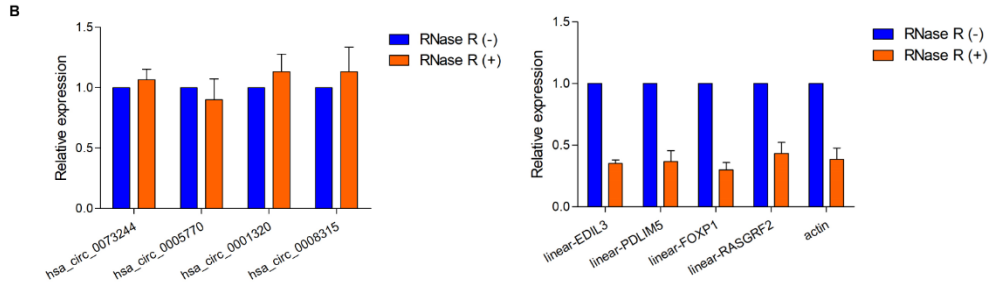
Supplementary Figure 2



Supplementary Figure 2. SMSCs surface-specific markers detection.
FCM analysis showed that more than 94% of the SMSCs were able to express CD105, CD44, CD90 and CD73, but the number of cells expressing CD11b, CD14, and CD34 was less than 2%.

Supplementary Figure 3

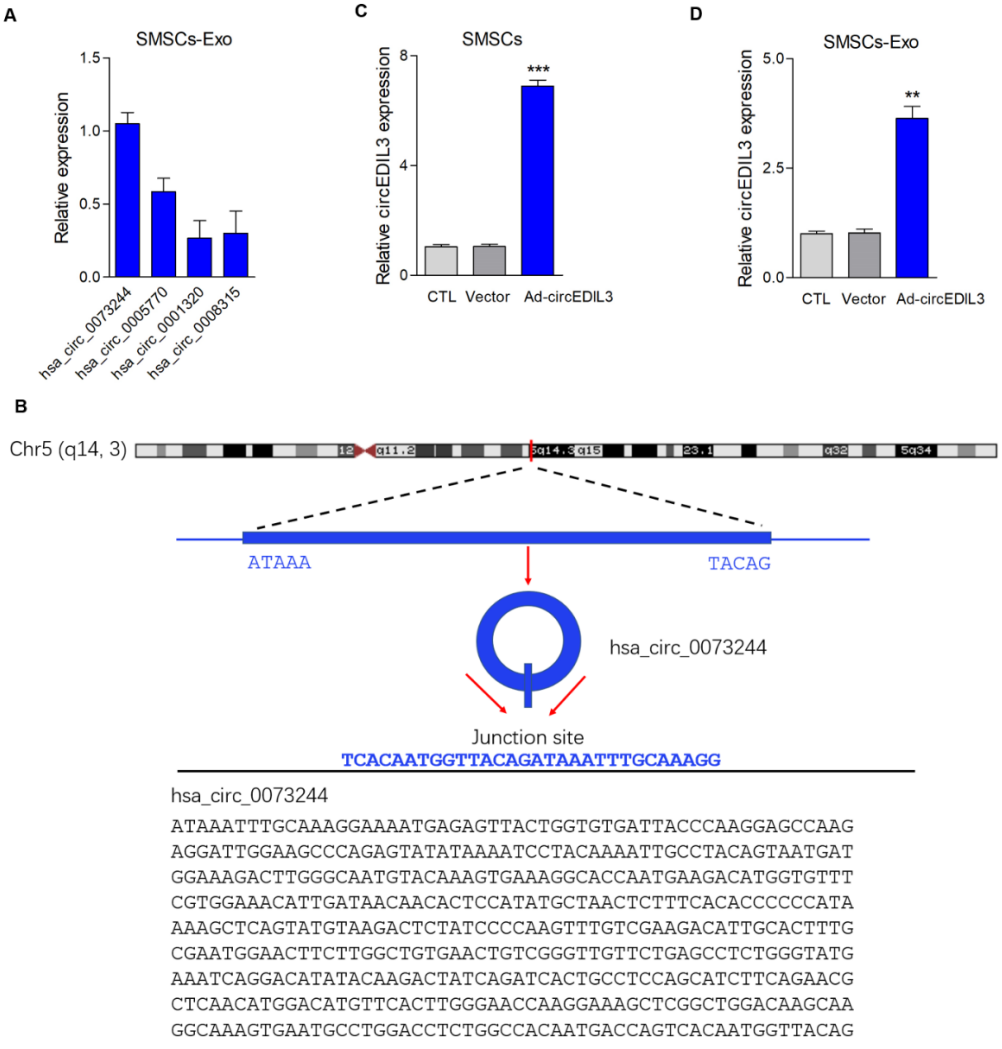




Supplementary Figure 3. Confirmation of significantly upregulated circRNAs expressed in SMSCs relative to RA-FLS.

(A) According to the previous article, we first selected 7 possible circular RNAs according to the relative transcriptional level of the top differentially highly expressed circRNAs, which were confirmed by qRT-PCR analysis of RNAs extracted from independent biological replicates of MSCs and skin fibroblasts. We found that 4 circRNAs (hsa_circ_0073244, hsa_circ_0005770, hsa_circ_0001320 and hsa_circ_0008315) had significantly higher expressions in SMSCs relative to RA-FLS via qRT-PCR analysis. (B) All the 4 circRNAs, hsa_circ_0073244, hsa_circ_0005770, hsa_circ_0001320 and hsa_circ_0008315 could resist RNase R's digestion, while their linear forms were digested by RNase R. Data are expressed as the mean ± S.E.M. n = 3, each group; *$p < 0.05$.

Supplementary Figure 4



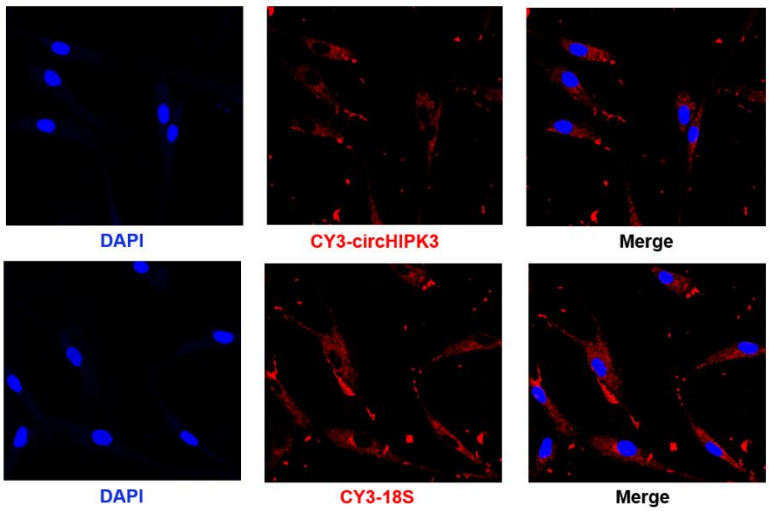
hsa_circ_0073244

ATAAATTTGCAAAGGAAAATGAGAGTTACTGGTGTGATTACCCAAGGAGCCAAG
AGGATTGGAAGCCCAGAGTATATAAAATCCTACAAAATTGCCTACAGTAATGAT
GGAAAGACTTGGGCAATGTACAAAGTGAAAGGCACCAATGAAGACATGGTGTTT
CGTGGAAACATTGATAACAACACTCCATATGCTAACTCTTTCACACCCCCCATA
AAAGCTCAGTATGTAAGACTCTATCCCCAAGTTTGTCGAAGACATTGCACTTTG
CGAATGGAACTTCTTGGCTGTGAACTGTCGGGTTGTTCTGAGCCTCTGGGTATG
AAATCAGGACATATACAAGACTATCAGATCACTGCCTCCAGCATCTTCAGAACG
CTCAACATGGACATGTTCACTTGGGAACCAAGGAAAGCTCGGCTGGACAAGCAA
GGCAAAGTGAATGCCTGGACCTCTGGCCACAATGACCAGTCACAATGGTTACAG

Supplementary Figure 4. Hsa_circ_0073244 (circEDIL3) expression in SMSCs-derived exosomes.

(A) CircEDIL3 was confirmed to be the most highly expressed one among four circRNAs in SMSCs-Exo. (B) The genomic location of the mEDIL3 gene and of hsa_circ_0073244 plus the sanger sequencing showing the "head-to-tail" splicing of hsa_circ_0073244. (C) CircEDIL3 was confirmed to be successfully overexpressed in adenovirus vector encoding circEDIL3 (Ad-circEDIL3) infected SMSCs via qRT-PCR analysis. (D) Exosomes from the culture supernatants of Ad-circEDIL3-transfected SMSCs (Ad-circEDIL3-SMSCs-Exo) carried significantly enhanced expression of circEDIL3. Data are expressed as the mean ± S.E.M. n = 3, each group; $^{**}p < 0.01$, $^{***}p < 0.001$.

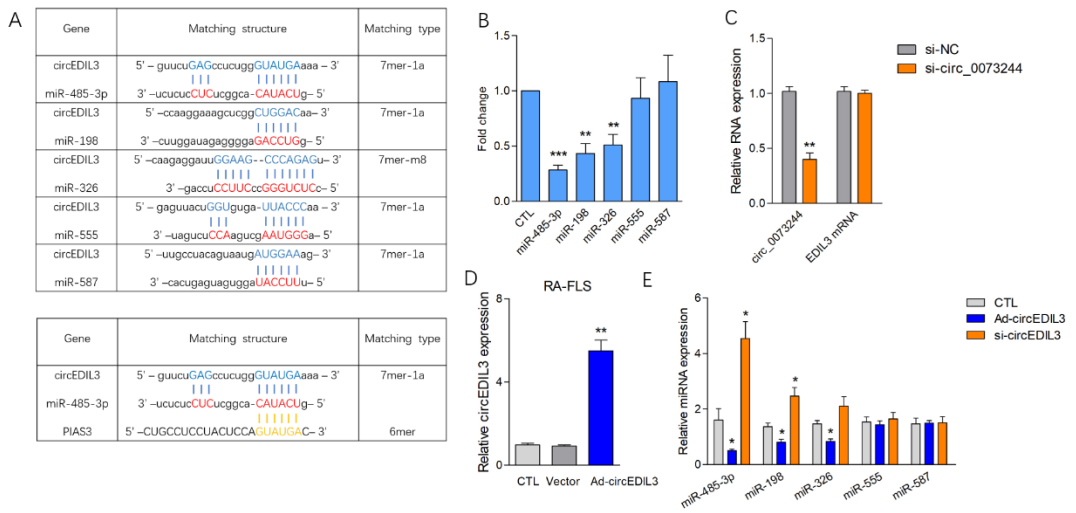
Supplementary Figure 5



Supplementary Figure 5. Location of circEDIL3 in cytoplasm.

Fluorescence in situ hybridization (FISH) results showed that circEDIL3 transcript signals were mostly located in the cytoplasm of RA-FLS.

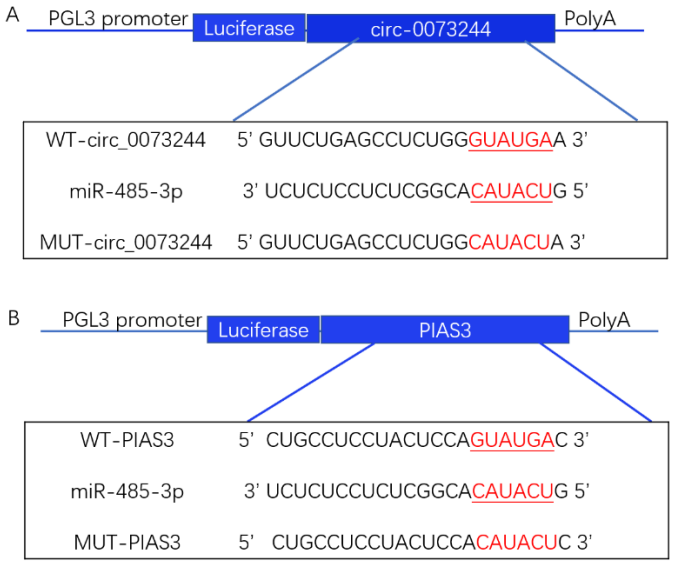
Supplementary Figure 6



Supplementary Figure 6. Screening target miRNAs of circEDIL3.

(A) At least one miRNA-binding site defined by Arraystar Proprietary Algorithms was confirmed using the CircInteractome database. The schematic graph illustrated binding sites between circEDIL3 and miR-485-3p, miR-485-3p and PIAS3 mRNA predicted by bioinformatics methods. (B) MiR-485-3p, miR-198 and miR-326 were able to reduce the Renilla luciferase reporter activity compared to the negative control. (C) The siRNA-mediated circ_0073244 knockdown was quite significant in RA-FLS but its linear transcript EDIL3 expression was not obviously affected by si-circ_0073244. Hence, the siRNA-mediated knockdown of circ_0073244 was highly specifc. (D) CircEDIL3 overexpression was successfully conducted in RA-FLS. (E) qRT-PCR analysis showed that upregulating circEDIL3 decreased miRNAs expression, while downregulating circEDIL3 increased miRNAs expression, and miR-485-3p was the most significant one. Data are expressed as the mean ± S.E.M. n = 3, each group; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

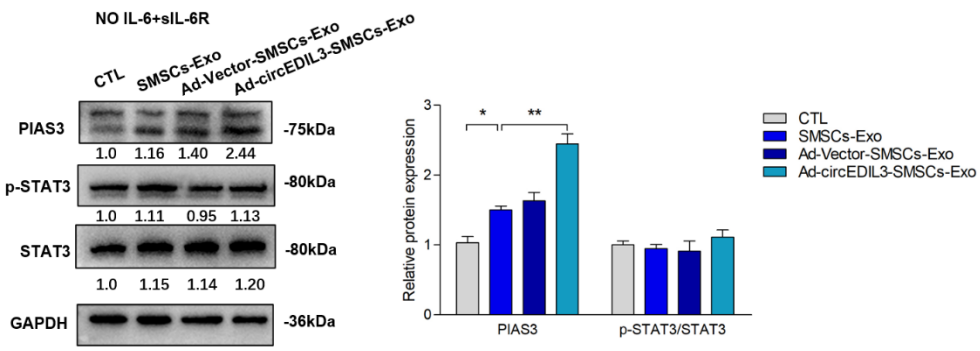
Supplementary Figure 7



Supplementary Figure 7. Mutant circEDIL3/PIAS3 sequences for luciferase reporter assay.

(A) Plasmids with wildtype or mutant circEDIL3 sequences were constructed to explore the correlation between circEDIL3 and predicted miR-485-3p. (B) Plasmids with wildtype or mutant PIAS3 sequences were constructed.

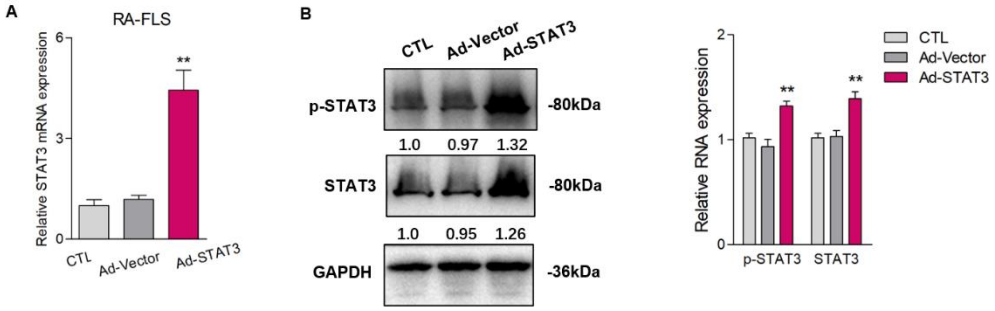
Supplementary Figure 8



Supplementary Figure 8. PIAS3 protein expression and STAT3 activity influenced by SMSCs-Exo or Ad-circEDIL3-Exo without IL-6+sIL-6R induction.

Western blot analysis showed that without IL-6+sIL-6R induction, PIAS3 protein expression could be promoted by SMSCs-Exo treatment compared with PBS, and futher upregulated by Ad-circEDIL3-Exo. However p-STAT3 and STAT3 protein levels as well as p-STAT3/STAT3 ratio didn't change signicantly. Data are expressed as the mean ± S.E.M. n = 3, each group; *$p < 0.05$, **$p < 0.01$.

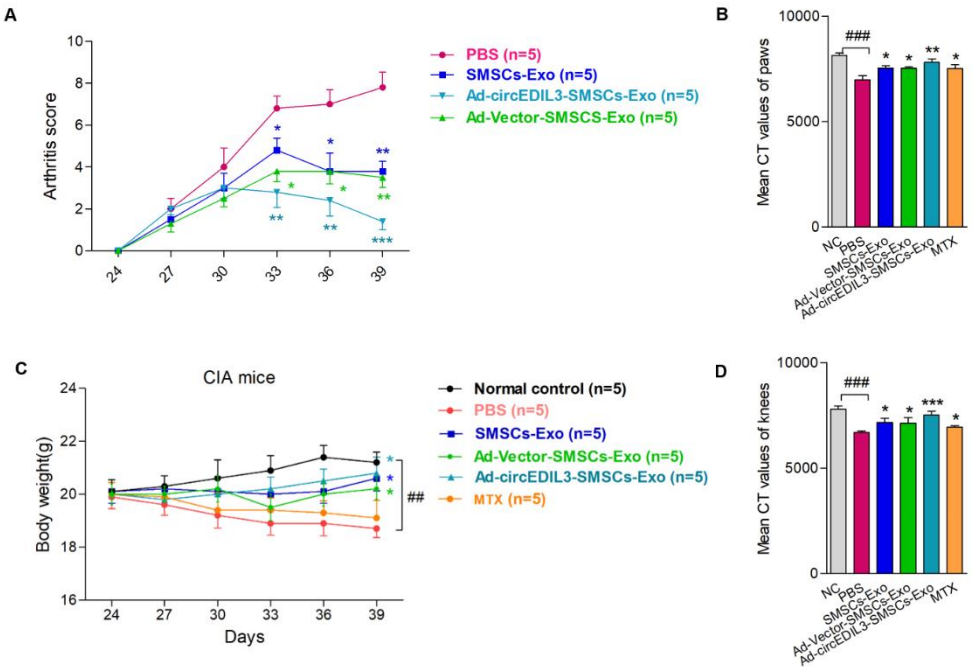
Supplementary Figure 9



Supplementary Figure 9. Successful overexpression of STAT3 in RA-FLS.

Moderate STAT3 was transfected into RA-FLS to augment the intracellular STAT3 thus p-STAT3 expression. STAT3 mRNA (A) and protein (B) expression were significantly upregulated by STAT3 overexpression. Data are expressed as the mean ± S.E.M. n = 3, each group; **$p < 0.01$.

Supplementary Figure 10



Supplementary Figure 10. Clinical arthritis scores in CIA mice treated with Ad-Vector-SMSCS-Exo, and mean body-weight of CIA mice under different treatment.

(A) Clinical arthritis scores of Ad-Vector-SMSCS-Exo group were shown. There was no significant difference of clinical arthritis scores between CIA mice treated with BMSCs-Exo and Ad-Vector-SMSCS-Exo. (B) Mean micro-CT values of paws were evaluated. Mean values were significantly decreased in CIA control mice compared to normal mice. Furthermore mean values of SMSCS-Exo, Ad-circEDIL3-SMSCS-Exo, MTX group were significantly increased compared with PBS treatment group, and interstingly, the increasement of mean values was more evident in Ad-circEDIL3-SMSCS-Exo group. micro-CT analysis also confirmed that bone erosions were similar when mice were injected with SMSCS-Exo or Ad-circEDIL3-SMSCS-Exo. (C) Mean body-weight of CIA mice under different treatment. (D) The changing trends of mean micro-CT values of knee joints were consistent with paws. Data are expressed as the mean ± S.E.M. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus PBS treatment group, ##$p < 0.01$, ###$p < 0.001$ versus NC. NC = normal control.

Supplementary Table 1 (Table S 1). Primers and probes used in the study.

Gene	Sequence
hsa_circ_0073244	5' –AATGACCAGTCACAATGGTTACAGA– 3' 3' –TCTTGGCTCCTTGGGTAATCAC– 5'
miR-485-3p	5' –CAGTCATACACGGCTCTCCTC– 3' 3' –CCAGTGCAGGGTCCGAGGT– 5'
STAT3	5′-CCAGTCAGTGACCAGGCAGAAAG-3′ 3′-GCACGTACTCCATCGCTGACA-5′
PIAS3	5′-GCCGACATGGACGTGTCCTGTG-3′ 3′-TTCCCTCCTGG ACTGCGCTGTAC-5′
VEGF	5' –TTCTGGGCTGTTCTCGCTTC– 3' 3' –CTCTCCTCTTCCTTCTCTTCTTCC– 5'
GAPDH	5' – GCACCGTCAAGGCTGAGAAC– 3' 3' –TGGTGAAGACGCCAGTGGA– 5'
U6	5′-GTAGATACTGCAGTACG-3′ 3′-ATCGCATGACGTACCTGAGC-5′

circRIP probes

hsa_circ_0073244	5'-CTCATTTTCCTTTGCAAATTTATCTCTAACCA TTGTGACTGGTC-3'-biotin
Control	5'-CTAAGACTAGGAGTTCGGCGGAACCACAAA AAGAGACCTCAGAA-3'-biotin

FISH probes	
hsa_circ_0073244	5'-CY3-TTTATCTGTAACCATTGTGACTGGTC-3'
siRNAs	
si-circ_0073244	5' –UAUCUGUAACCAUUGUGACUG– 3'
si-NC	5′- UUCUCCGAACGUGUCACGU-3′
miR-485-3p mimic	RiboBio
miR-485-3p inhibitor	RiboBio