Original Article

ADNCR modulates neural stem cell differentiation and proliferation through the regulation of TCF3 expression

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Background: Neural stem cells (NSCs) are undifferentiated precursor cells that have the ability to self-renew and proliferate and have the capacity to become either glia (oligodendrocytes and astrocytes) or neurons. NSCs can act as beneficial adjuncts for many neurological disorders, such as cerebral infarction, spinal cord injuries, Alzheimer's disease, and Parkinson's disease. Long noncoding RNAs (lncRNAs) play essential roles during cell differentiation, proliferation, and metabolism. This study aimed to explore the role played by adipocyte differentiation-associated long noncoding RNA (ADNCR) in the self-renewal and multipotency of NSCs.

Methods: In this study, we identified NSCs and verified that these cells were able to regenerate and differentiate into both astrocytes and neurons. Then we studied the relation between expression of ADNCR and transcription factor 3 (TCF3) and proliferation of NSCs.

Results: ADNCR and TCF3 expression have been shown to decrease during the differentiation of NSCs into both neurons and astrocyte induction cells. However, the expression of the microRNA miR-204-5p increased over time during the differentiation of NSCs into both neurons and astrocyte induction cells. ADNCR acts as a competing endogenous RNA (ceRNA) for miR-204-5p, and the overexpression of ADNCR suppressed miR-204-5p expression and enhanced TCF3 expression in NSCs, which resulted in enhanced proliferation and suppressed neural differentiation.

Conclusions: These data suggested that the use of ADNCR may represent a new strategy for expanding the interventions used to treat neurological disorders.

Keywords: Adipocyte differentiation-associated long noncoding RNA (ADNCR); long noncoding RNAs (lncRNAs); transcription factor 3 (TCF3); miR-204-5p

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Introduction

Neural stem cells (NSCs) are undifferentiated precursor cells that have the ability to self-renew and proliferate and have the capacity to become either glia (oligodendrocytes and astrocytes) or neurons (1-3). NSCs have been widely investigated for potential clinical uses (4-6). Several studies have suggested that NSCs can act as beneficial adjuncts and could potentially be used to treat for many neurological disorders, such as cerebral infarction, spinal cord injuries, Alzheimer's disease, Parkinson's disease, epilepsy, and neurasthenia (4,7-10). Although the functional characteristics of NSCs have been widely investigated, the molecular mechanisms underlying NSC migration, differentiation and self-renewal remain unknown (11-13). Thus, studying the molecular mechanisms that modulate migration, differentiation and self-renewal is crucial to understanding the determinants of NSC cellular fates.

Long noncoding RNAs (lncRNAs) are RNAs that are longer than two hundred nucleotides (nts) in length and belong to one class of noncoding RNAs (ncRNAs) (14-17). Recent studies have revealed that several lncRNAs play essential roles in a large range of functions, including cell fate, differentiation, proliferation, invasion, and metabolism (18-21). The expression of many lncRNAs was found to be dysregulated during human diseases, such as tumor, intervertebral disc degeneration, spinal cord injuries, and Parkinson's disease (22-25). Recently, growing evidence has suggested that lncRNAs also play roles in the development, self-renewal, and differentiation of NSCs (26-28). A new lncRNA, adipocyte differentiation-associated long noncoding RNA (ADNCR), was recently identified and found to suppress the differentiation of adipocytes (29). However, the role played by ADNCR in the self-renewal and multipotency of NSCs remains unknown.

In our study, we first identified NSCs and found that these cells could regenerate and differentiate into both astrocytes and neurons. ADNCR expression was found to decrease during the differentiation of NSCs into both neurons and astrocyte induction cells. The ectopic expression of ADNCR suppressed the proliferation of NSCs and the differentiation of NSCs into neurons.

Methods

Cell culture and transfection

Primary NSCs were cultured using a modified method based on previously published protocols (26,30). Primary NSCs were isolated from 13.5-day rat embryos and maintained in DMEM medium, supplemented with N2, epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF, R&D). pcDNA-control, pcDNA-ADNCR, miR-NC, miR-204-5p, siRNA-control, and siRNA-transcription factor 3 (TCF3) were acquired from Ambion (Thermo). These vectors were transfected into primary NSCs using Lipofectamine 3000 (Invitrogen, USA), according to the manufacturer's instructions.

Immunocytochemistry

Cells were first fixed with 4% paraformaldehyde and permeabilized with Triton-X100 (0.2%). After blocking in 10% serum, the cells were treated with mouse anti-β-tubulin III monoclonal antibody (clone SDL.3D10, RRID:AB_2210370; Catalog No. T8660; Sigma-Aldrich), at 4 ℃ for 12 hours, and followed by incubation with secondary antibodies.

Cell proliferation

Cell growth was determined using Cell Counting kit 8 (CCK8) analysis (Dojindo, Japan), according to the manufacturer's instructions. The growth rate was analyzed at different time points after transfection. The absorbance was detected at 450 nm by a microplate reader.

qRT-PCR

Total RNA was extracted from the cells using a TRIzol kit (Invitrogen, CA, USA). The expression levels of miRNA, lncRNA and mRNA were determined by quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR) analysis using SYBR Green (QIAGEN, Germany) on a 7500 PCR detection system (Applied Biosystems, Thermo). The primers used were as follows: β-tubulin III, 5'-AGCAAGGTGCGTGAGGAGTA-3' and 5'-TCTAGTGTCTCATGGCTCTGGTTTT-3'; Nestin, 5'-GATCTAAACAGGAAGGAAATCCAGG-3' and 5'-TCTAGTGTCTCATGGCTCTGGTTTT-3'; GAPDH, 5'-CTCCTCCTGTTCGACAGTCAGC-3' and 5'-CCCAATACGACCAAATCCGTT-3'. The data are shown as $2^{-\Delta\Delta CT}$ means.

Western blot

Cells were lysed with cell lysis buffer (Pierce, Thermo

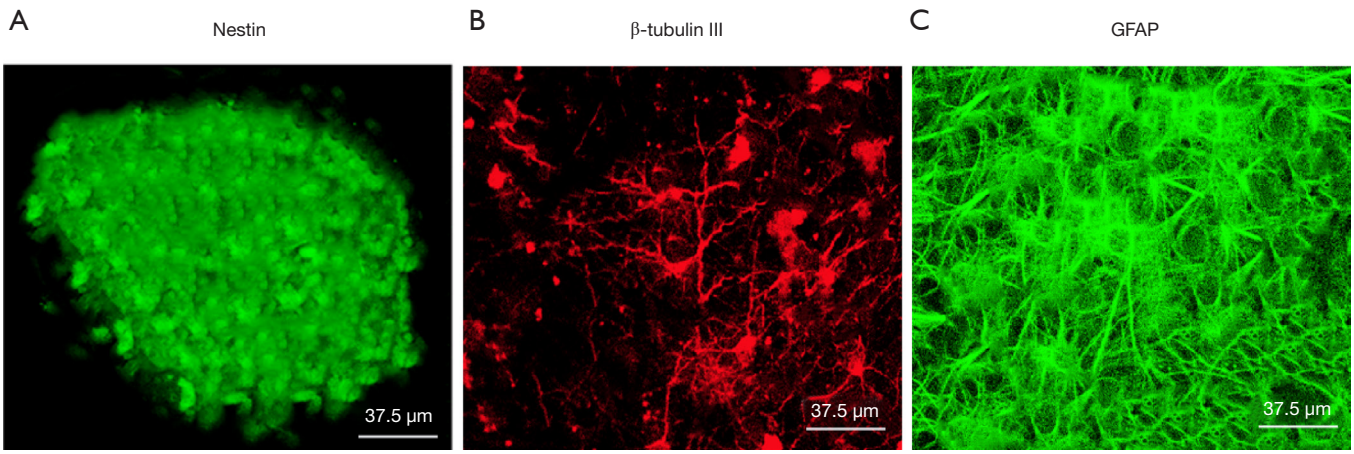

Figure 1 NSCs have regenerative abilities and can differentiate into astrocytes and neurons. (A) Cells were immunostained with the NSC-marker nestin; (B) differentiated cells, immunostained with the neuron-specific marker β-tubulin III; (C) differentiated cells, immunostained with the astrocyte-specific marker GFAP. NSC, neural stem cell; GFAP, glial fibrillary acidic protein.

Fisher Scientific) to obtain total protein. Protein was resolved on a 10% SDS-PAGE gel and then transferred into a polyvinylidene difluoride (PVDF) membrane. The membrane was blocked with milk for 2 hours and then blotted with mouse anti-β-tubulin III monoclonal antibody (clone SDL.3D10, RRID: AB_2210370; Catalog No. T8660; Sigma-Aldrich), mouse anti-TCF3 monoclonal antibody (clone 5G2, RRID: AB_2255610; Catalog No. SAB1404452; Sigma-Aldrich) and Mouse anti-GAPDH monoclonal antibody (clone CL3266, RRID: AB_10597731; Catalog No. AMAB91153; Sigma-Aldrich). The blot was incubated with secondary antibodies, and an ECL kit (Millipore, USA) was used to visualize the proteins. GAPDH was used as a loading control.

Luciferase reporter assay

The mutant (Mut) or wild-type (WT) 3'UTR of TCF3 was cloned into the pGL3-luciferase reporter vector (Promega, USA). NSCs were co-transfected with miR-204-5p mimic or miR-NC, and Mut or WT TCF3 3'UTR, and Renilla luciferase (Promega, USA), using Lipofectamine 3000 (Invitrogen, USA). Luciferase activity was determined with the Dual-Luciferase kit, according to the manufacturer's instructions.

Statistical analysis

The results are presented as the mean ± SD (standard deviation), and statistical analyses were performed using SPSS. Student's *t*-test was used to measure significant differences between two groups. A P value of <0.05 was defined as statistically significant.

Results

NSCs have regenerative abilities and can differentiate into astrocytes and neurons

Isolated NSCs have regenerative abilities and can be shaped into neurospheres, which were positive for nestin (*Figure 1A*), which is a specific marker for NSCs. After the removal of bFGF, FBS, and EGF, the NSCs differentiated into astrocytes and neurons, which were identified by immunostaining using the neuron-specific marker β-tubulin III (*Figure 1B*) and the astrocyte-specific marker glial fibrillary acidic protein (GFAP) (*Figure 1C*).

Decreased ADNCR and TCF3 and increased miR-204-5p expression levels during NSC differentiation

To study the functional role of ADNCR during the differentiation of NSCs, we measured ADNCR expression levels during NSC differentiation using qRT-PCR. The data showed that ADNCR expression decreased during the differentiation of NSCs into both neurons (*Figure 2A*) and astrocytes (*Figure 2B*). In addition, the expression level of miR-204-5p increased over time during the differentiation

of NSCs into both neurons (*Figure 2C*) and astrocytes (*Figure 2D*). Moreover, TCF3 was downregulated during the differentiation of NSCs into both neurons (*Figure 2E*) and astrocytes (*Figure 2F*).

ADNCR acts as a competing endogenous RNA (ceRNA) for miR-204-5p and regulates TCF3 expression

ADNCR expression was upregulated in NSCs transfected with the pcDNA-ADNCR vector (*Figure 3A*). The miR-204-5p expression levels increased in the NSCs after transfection with the miR-204-5p mimic (*Figure 3B*). We used bioinformatics analysis to show that TCF3 is a potential target for miR-204-5p (*Figure 3C*). The dual-luciferase reporter assay showed that the ectopic expression of miR-204-5p decreased the luciferase activity of WT TCF3 3'-UTR but not Mut TCF3 3'-UTR (*Figure 3D*). The overexpression of ADNCR inhibited miR-204-5p expression, according to the qRT-PCR analysis (*Figure 3E*). The ectopic expression of ADNCR enhanced TCF3 expression, as assessed by western blot (*Figure 3F*).

The ectopic expression of ADNCR promoted cell proliferation and suppressed the neuronal differentiation of NSCs

As shown in *Figure 4A*, the elevated expression of ADNCR enhanced NSC growth, as assessed by the CCK-8 assay. In addition, ectopic ADNCR expression increased nestin expression in NSCs (*Figure 4B*). Furthermore, our data showed that β-Tubulin III expression was inhibited in neural induction cells treated with pcDNA-ADNCR (*Figure 4C,D*). The immunocytochemical staining of β-Tubulin III also indicated that the overexpression of ADNCR suppressed NSC neuronal differentiation (*Figure 4E*).

The inhibition of TCF3 expression abolishes the effects of ADNCR overexpression on NSC differentiation and proliferation

To further confirm the contributions of TCF3 to the functions of ADNCR during NSC differentiation and proliferation, we suppressed TCF3 expression in ADNCR-overexpressing NSCs. As shown in *Figure 5A*, TCF3 expression was downregulated in NSCs after treatment with siRNA-TCF3. We also found that the protein expression of TCF3 was decreased in NSCs after treatment with siRNA-TCF3 (*Figure 5B*). By using CCK-8 analysis, the results indicated that the knockdown of TCF3 expression suppressed cell growth in ADNCR-overexpressing NSCs (*Figure 5C*). The inhibition of TCF3 expression also decreased nestin expression in ADNCR-overexpressing NSCs (*Figure 5D*). Furthermore, the knockdown of TCF3 expression promoted β-Tubulin III expression in ADNCR-overexpressing NSCs (*Figure 5E*). In addition, the immunocytochemical staining of β-Tubulin III also showed that the suppression of TCF3 enhanced NSC differentiation into neurons (*Figure 5F*).

Discussion

In our study, we first identified NSCs and determined that these cells have regenerative abilities and can differentiate into astrocytes and neurons. ADNCR and TCF3 expression levels decreased during the differentiation of NSC into both neural and astrocyte induction cells. However, the expression of miR-204-5p increased over time during the differentiation of NSCs into both neural and astrocyte induction cells. The ectopic expression of ADNCR induced cell proliferation and suppressed the neuronal differentiation of NSCs. ADNCR acts as a ceRNA for miR-204-5p, and the overexpression ADNCR suppressed miR-204-5p expression and enhanced TCF3 expression in NSCs. The ectopic expression of ADNCR induced NSC proliferation and suppressed the neuronal differentiation of NSCs, partly by regulating miR-204-5p/TCF3 expression.

NSCs share two requisite properties with all stem cells, self-renewal, and multipotency, and they can differentiate into both astrocytes and neurons (3,31,32). The differentiation and maintenance of NSCs are tightly regulated by molecular networks (33,34). Recently, the functions of lncRNAs during the control of NSCs self-renewal and multipotency has been investigated. Zhang *et al.* (35) showed that the lncRNAs Rik-203 and Rik-201 suppressed neural differentiation via the regulation of miR-467a-3p and miR-96, respectively. Li and colleagues found that the lncRNA lnc158 increased the differentiation of neural precursor cells into oligodendrocytes by modulating nuclear factor-IB (36). Winzi *et al.* demonstrated that the lncRNA lncR492 suppressed embryonic stem cell differentiation into neurons (37). In addition, Li *et al.* reported that the novel lncRNA ADNCR suppressed the differentiation of adipocytes (29). However, the role played by ADNCR in the self-renewal and multipotency of NSCs

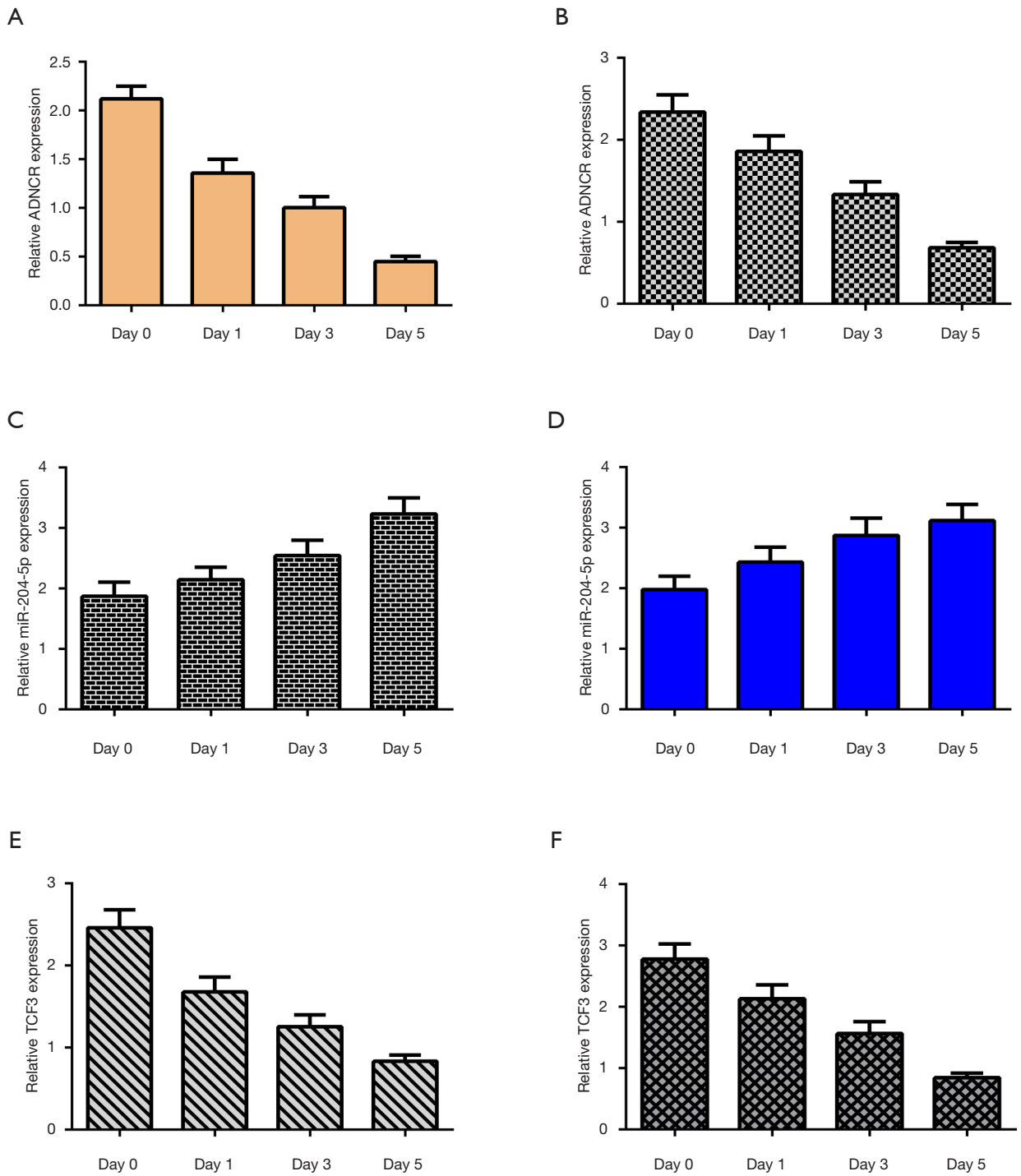

Figure 2 Decreased ADNCR and TCF3 and increased miR-204-5p expression levels during the differentiation of NSCs. (A) ADNCR expression was decreased during the differentiation of NSCs into neuron induction cells; (B) the expression of ADNCR was measured by qRT-PCR assay; (C) the expression levels of miR-204-5p increased over time during the differentiation of NSCs into neuron induction cells; (D) the expression of miR-204-5p was measured by qRT-PCR assay; (E) the expression level of TCF3 was decreased during the differentiation of NSCs into neuron induction cells; (F) the expression of TCF3 was determined by qRT-PCR assay. ADNCR, adipocyte differentiation-associated long noncoding RNA; NSC, neural stem cell; TCF3, transcription factor 3.

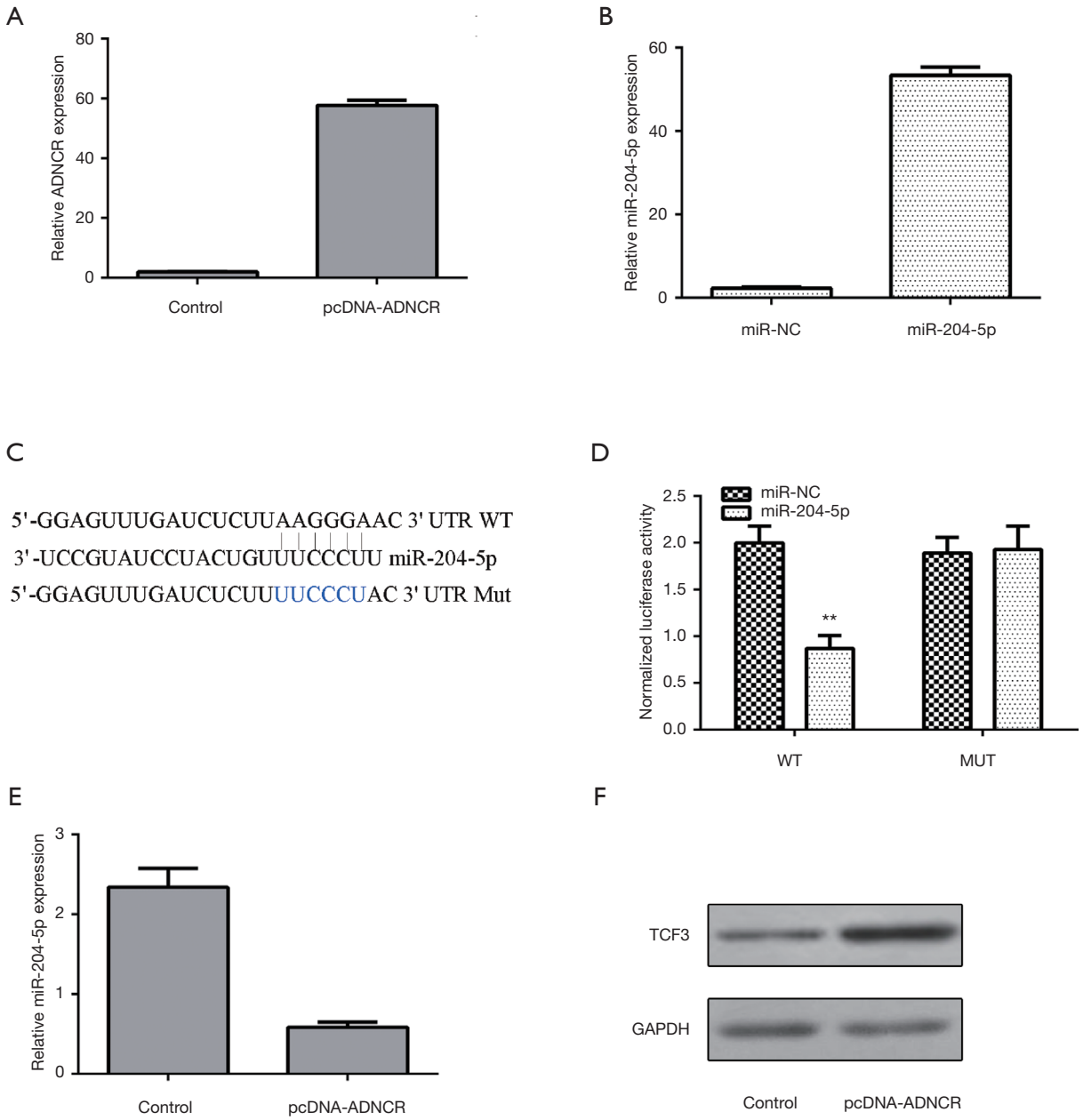

Figure 3 ADNCR acts as a ceRNA for miR-204-5p and regulates TCF3 expression. (A) The expression of ADNCR was detected by qRT-PCR assay; (B) the expression of miR-204-5p was measured by qRT-PCR assay; (C) TCF3 is a potential target of miR-204-5p, according to the results of the dual-luciferase reporter assay; (D) the ectopic expression of miR-204-5p decreased luciferase activity of WT (wild-type) TCF3 3'-UTR but not Mut (mutated) TCF3 3'-UTR; (E) the overexpression of ADNCR inhibited miR-204-5p expression, as assessed by qRT-PCR; (F) the ectopic expression of ADNCR enhanced TCF3 expression, as assessed by western blot. **, P<0.01. ADNCR, adipocyte differentiation-associated long noncoding RNA; TCF3, transcription factor 3.

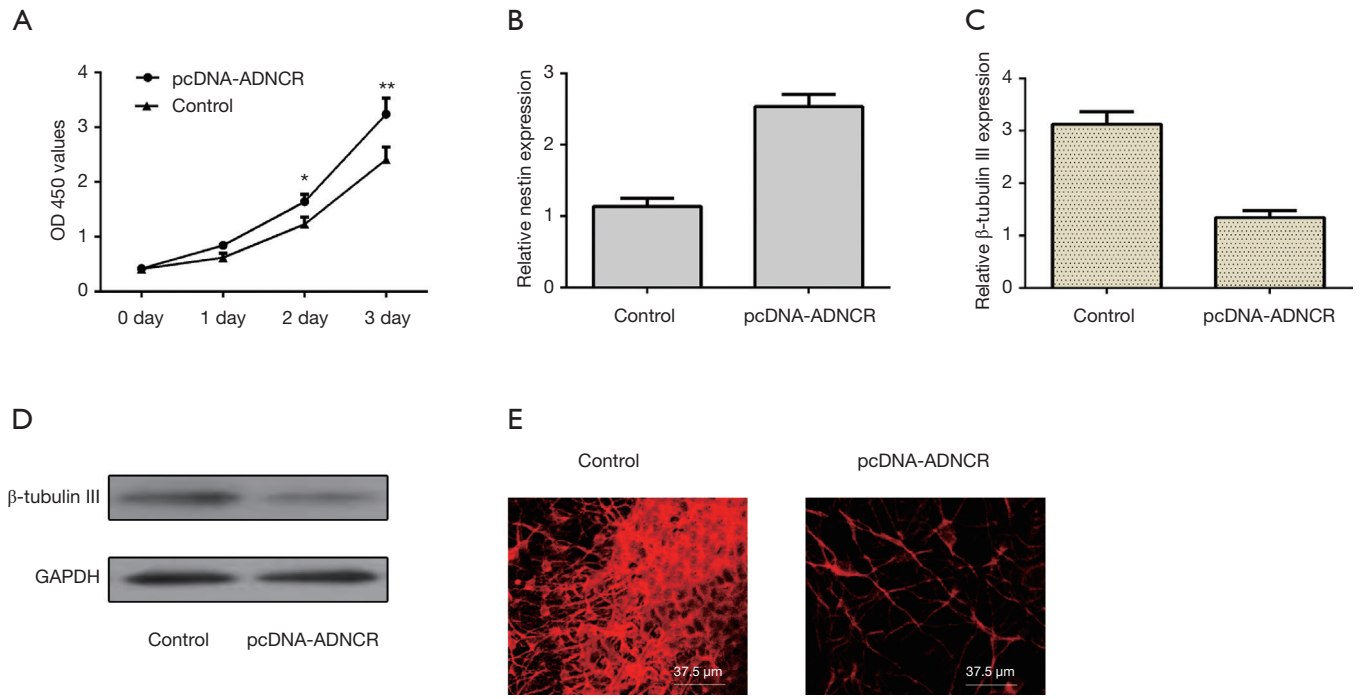

Figure 4 Ectopic expression of ADNCR promoted NSC proliferation and differentiation into neurons. (A) Increased expression of ADNCR promoted NSCs growth, as assessed by CCK-8 assay; (B) the expression of nestin was determined by qRT-PCR analysis; (C) β-Tubulin III expression was inhibited in neural induction cells treated with pcDNA-ADNCR; (D) the protein expression of β-Tubulin III was determined by western blot; (E) the immunocytochemical staining of β-Tubulin III also indicated that the overexpression of ADNCR suppressed NSC differentiation into neurons. *, P<0.05; **, P<0.01. ADNCR, adipocyte differentiation-associated long noncoding RNA; NSC, neural stem cell.

remains unknown. In this study, ADNCR expression was shown to decrease during the differentiation of NSCs into both neuron and astrocyte induction cells. The ectopic expression of ADNCR enhanced NSC proliferation and suppressed NSC differentiation into neurons.

Previous studies indicated that TCF3 played important functional roles associated with the modulation of neurogenesis (38). TCF3 acted as a suppressor of Wnt expression and functions as an activator of β-catenin (39). For instance, Kuwahara *et al.* (40) demonstrated that TCF3 expression was downregulated in cells that differentiate into neurons. TCF3 maintains populations by inhibiting the Wnt/β-catenin signal pathway during neocortical development. Wang and colleagues found that miR-506-3p modulated NSC differentiation and proliferation by regulating TCF3 expression (3). In our study, we found that TCF3 expression decreased during the differentiation of NSCs into both neuron and astrocyte induction cells. We used bioinformatics analysis to show that TCF3 is a potential target of miR-204-5p. In a dual-luciferase reporter assay, the ectopic expression of miR-204-5p decreased the luciferase activity of WT TCF3 3'-UTR but not Mut TCF3 3'-UTR. The overexpression of ADNCR inhibited the expression of miR-204-5p and enhanced the expression of TCF3. The ectopic expression of ADNCR enhanced NSC proliferation and suppressed NSC differentiation into neurons, partly via the regulation of TCF3 expression.

In summary, our data revealed that both ADNCR and TCF3 expression decreased during the differentiation of NSCs into both neuron and astrocyte induction cells, and the ectopic expression of ADNCR enhanced NSC proliferation and suppressed NSC differentiation into neurons, partly via the regulation of TCF3 expression. These data suggested that the use of ADNCR may represent a new strategy for expanding the interventions used to treat neurological disorders.

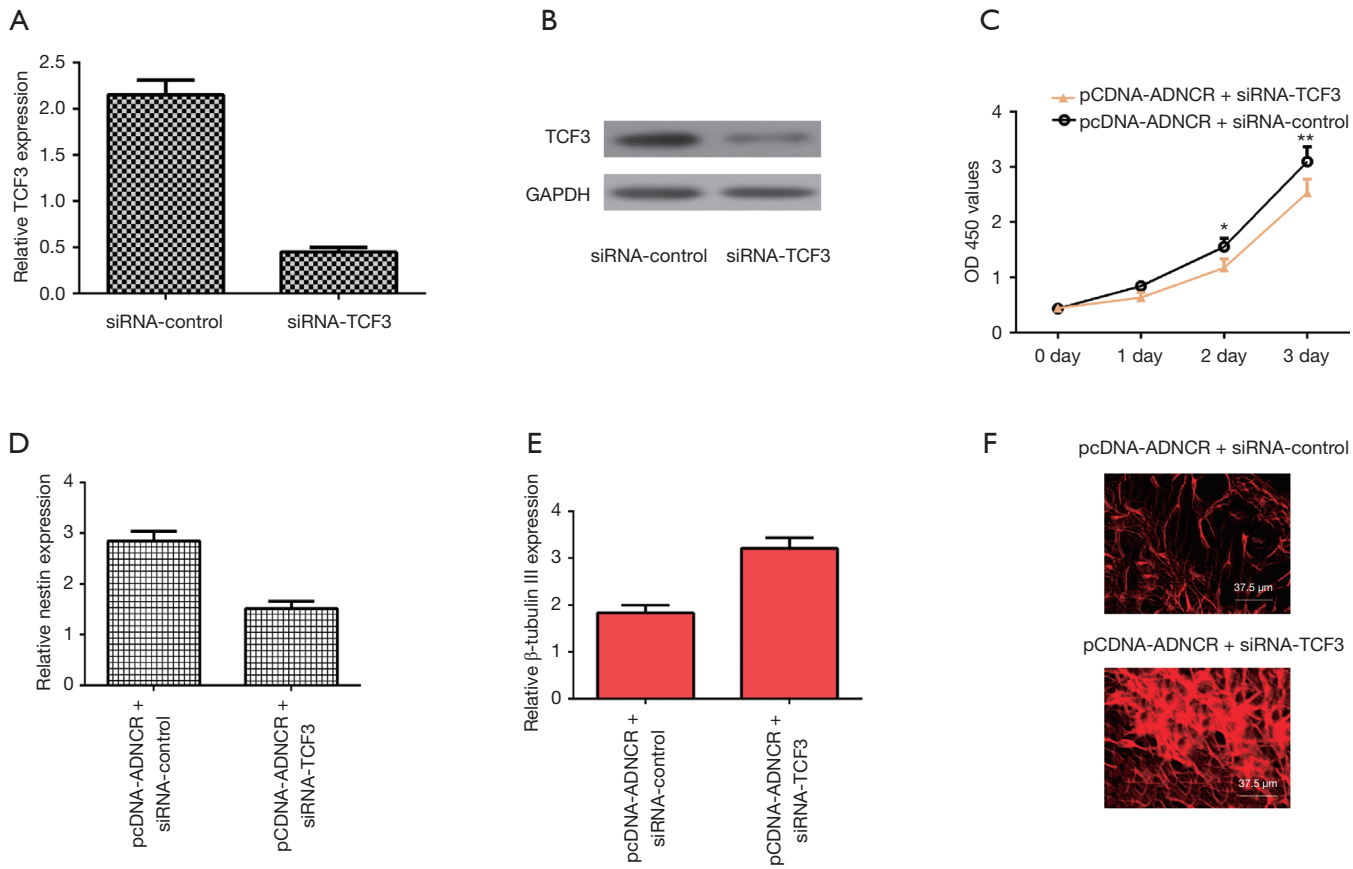

Figure 5 Inhibition of TCF3 expression abolishes the effects of ADNCR overexpression on NSC differentiation and proliferation. (A) The expression of TCF3 was analyzed by qRT-PCR assay; (B) the protein expression of TCF3 was determined by western blot; (C) CCK-8 analysis results indicated that the knockdown TCF3 expression induced cell growth in ADNCR-overexpressing NSCs; (D) the expression of nestin was detected by qRT-PCR assay; (E) the expression of β-Tubulin III was determined by qRT-PCR assay; (F) immunocytochemical staining of β-Tubulin III also showed that the suppression of TCF3 enhanced NSC differentiation into neurons. *, P<0.05; **, P<0.01. TCF3, transcription factor 3; ADNCR, adipocyte differentiation-associated long noncoding RNA.

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Footnote

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-1068

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-1068). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The need for ethics approval and consent of the present study was waived by Third Affiliated Hospital of Sun Yat-sen University.

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