Mesenchymal stem cell-derived exosomes would exert neuroprotective effect via regulating autophagic flux and alpha-synuclein expression in Parkinsonian models

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Mesenchymal stem cell-derived exosomes would exert neuroprotective effect via regulating autophagic flux and alpha-synuclein expression in Parkinsonian models

Directed by Professor Phil Hyu Lee

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<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

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(Directed by Professor Phil Hyu Lee)

Parkinson's disease (PD) is a chronic neurodegenerative disease characterized by the selective loss of dopaminergic neurons and the presence of Lewy bodies composed of α-synuclein in the substantia nigra. Ample evidence suggests that abnormal expression and accumulation of α-synulcien plays a central role in pathogenesis of PD. Thus, the inhibition of α-synuclein accumulation by enhancing autophagy flux and modulation of α-synuclein expression could be a therapeutic strategy for PD treatment. In the present study, we investigated whether mesenchymal stem cells (MSCs)-derived exosomes reduce the levels of α-synuclein by enhancing autophagy and modulates α-synuclein expression in parkinsonian models. In preformed fibrils (PFF)-treated neuronal cells, treatment of MSCs-derived exosomes increased cellular viability, reduced the level of α-synuclein and enhanced the number of LC3-II-positive autophagosomes compared with cells treated PFF only. In animal model using adeno-associated virus vectors to overexpress αSyn (AAV-αSyn), injection of MSCs-derived exosomes decreased the expression of α-synuclein in the substantia nigra. In addition, in cellular models using MPP^+ neurotoxin, co-culture with MSCs and treatment of MSCs-derived exosomes downregulated expression of α-synuclein compared with cells treated with MPP^+ only. These findings suggest that MSCs derived exosomes promote αSyn clearance through enhancement of autophagy and have the potential to modulate α-synuclein expression in PD models.

Key words : parkinson’s disease, α-synuclein, MSCs, exosome, autophagy, regulation

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I. INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative disease characterized by the selective loss of dopaminergic neurons and the presence of Lewy bodies composed mainly of alpha-synuclein (αSyn) in the substantia nigra[1]. Although the initial triggering factors of PD remain unknown, ample evidence has shown that αSyn plays a critical role in the pathogenesis of PD[2]. In addition, dysfunction in cellular clearing systems may lead to αSyn accumulation.[3,4]

Autophagy is an essential catabolic mechanism in which cells degrade misfolded proteins and larger cellular complexes such as excessive organelles. In the pathogenesis of PD, Autophagic flux is important for the degradation of abnormal αSyn aggregates considering their critical role in maintaining αSyn homeostasis. Ample evidence has reported that impairment of autophagy may lead to αSyn accumulation and degeneration of dopaminergic neurons in PD.[5-7] Thus, modulation of autophagy might be a therapeutic strategy for PD.

Another approach to control abnormal accumulation of αSyn would be to modulate expression of αSyn. Since αSyn gene duplication and triplication can cause PD[8,9], reducing αSyn production could be a rational therapeutic implication. Thus, regulation of the

expression of αSyn might be another therapeutic strategy for PD.[10-12]

Mesenchymal stem cells (MSCs) are multipotent stem cells that can be differentiated into different lineages under the appropriate induction conditions. Ample evidence has suggested that MSCs is one of the candidates for a therapeutic strategy in PD considering their ability to modulate αSyn related microenvironments via pleiotropic effects[13-17]. However, there are obstacles concerning about a low survival rate of transplanted cells, which would make it difficult for researchers to control for cell viability and differentiation[18,19]. Recently, MSCs-derived exosomes have been proposed as a promising therapeutic alternative due to their therapeutic competence for regeneration and ability to maintain the therapeutic benefits of their origin cells without the risks associated with stem cell-based therapy[20-23]. Our previous studies demonstrated that MSCs contribute to alpha synuclein degradation by enhancing autophagy. In the present study, we set up the hypothesis as follows. Firstly, we hypothesized that MSCs-derived exosomes would exert neuroprotective effects through modulation of autophagy in parkinsonian models. To prove this, I evaluated whether treatment of MSCs-derived exosomes inhibits αSyn acuumulation and increases clearance of αSyn in cellular and animal models of PD. Secondly, my hypothesis is that MSCs and MSCs-derived exosomes would have potential to modulate αSyn expression in PD model. Thus, I investigated whether MSCs and MSCs-derived exosomes regulate protein expression of αSyn by modifying transcription of αSyn gene in cellular models of PD.

II. MATERIALS AND METHODS

1. MSCs and SH-SY5Y culture

Frozen vials of human bone marrow derived MSCs were obtained from the Corestem (South Korea). MSCs were maintained in low glucose Dulbecco's Modified Eagle Medium (DMEM; HyClone) supplemented with 10% fetal bovine serum (FBS; HyClone) and an antibiotic mixture of 1% penicillin and streptomycin (P/S; Corning). Especially MSCs were kept under the passage of 10 because prolonged subculture and later passage lead to lower levels of their capacity and stemness.

SH-SY5Y cells, the human neuroblastoma cell line, were obtained from the Korean Cell Line Bank (South Korea). SH-SY5Y cells were maintained in Dulbecco's Modified Eagle Medium (DMEM, Hyclone) supplemented with 10% fetal bovine serum (JC bio) and an antibiotic mixture of penicillin and streptomycin (1%,Hyclone). When the cells had 70-80% confluence, they were trypsinized and subcultured. Cells were maintained at a temperature of 37℃ in a humidified atmosphere containing 5% CO_2.

2. Co-culture and treatment

In the first experiment, SH-SY5Y cells were treated PFF (5uM) for 24hours in a humidified incubator at 37℃ and 5% CO2. Subsequently, the media was refreshed and the cells were treated with MSC and MSCs-derived exosomes. To evaluate the effects of MSCs, they were cultured on the permeable membrane of a transwell insert, and SH-SY5Y cells were cultured on the bottom of 6well plate. The plates were incubated at 37℃ and 5% CO2 for 24, 48 hours. In the second experiment, SH-SY5Y cells were treated MPP+ (2mM) for 48hours in a humidified incubator at 37℃ and 5% CO2. For inhibition of autophagy, either 20nM bafilomycin A1(Sigma) was added to the media.

3. Pre-formed fibrillary α-Syn preparation

Recombination α-Syn (5mg/ml in phosphate buffered saline(PBS) containig 50mM Tris and 100mM NaCl) was agitated at 37 ℃ (1000rpm) for 5days. The fibrillary form of α-Syn was visualized after agitation using electron microscopy. Confirmed preformed fibrillary

form (pff) of protein was briefly sonicated to allow it to readily internalize into cells. The fibrillary form of α-Synuclein was visualized after agitation using electron microscopy.

4. Isolation of exosomes

Vials of MSCs-derived exosomes were obtained from the S&E bio (South Korea). Isolation of exosomes was performed in biological safety cabinet (BSC). MSCs culture medium was collected by gentle pipetting at the top of the wells. To remove cell debris and apoptotic bodies, 1800 mL of culture medium was centrifuged at 2500 × *g* for 10 min, followed by filtration through a 0.22-μm membrane. The filtered medium was separated using a 300-kDa MWCO mPES hollow fiber MiniKros filter module (Spectrum Laboratories, Rancho Dominguez, CA, USA) on a commercially available KrosFlo KR2I tangential flow filtration (TFF) system (Spectrum Laboratories, Rancho Dominguez) that allows for large-scale processing of samples. The exosomes-containing sample was recirculated into the filtration bottle. Small molecules, including free protein, were passed through the membrane pores, eluted as permeate, and collected. The collected solution was used as a secretome. exosomes were maintained in circulation as retentate and concentrated in the bag. The shear rate of the feed stream was maintained between 3000 s−1 and 6000 s−1; trans-membrane pressure was performed 7.5 psi. We conducted 5 volume exchanges of exosomes with PBS and exosomes were subsequently concentrated into a final volume of 300 mL of recovery solution (PBS). The recovered solution was filtered through a 0.22-μm membrane. After harvesting the conditioned media, exosomes isolation process was immediately started with TFF procedure.

5. animal study

All procedures were performed in accordance with the Laboratory Animals Welfare Act, the Guide for the Care and Use of Laboratory Animals and the Guidelines and Policies for Rodent experiment provided by IACUC (Institutional Animal Care and Use Committee) in the Yonsei University Health System. Male C57BL/6J mice (5 weeks old) were acclimated in a climate-controlled room with a constant 12 h light/dark cycle (12 h on, 12 h off) for a

week prior to the experiment. At 6 weeks of age, the mice were randomly divided into three groups: Control group; AAV-αSyn group; AAV-αSyn + MSCs-derived exosomes treatment group. Briefly, the mice were anesthetized with isoflurane (Baxter) and the viruses were slowly injected into the SN(–3.1 mm posterior to bregma, ± 1.2 mm lateral to midline, and –4.3 mm ventral to the brain surface) using a stainless steel (26-gauge) injection needle connected to a 1 ml microsyringe (Hamilton). The needle was left in place for 10 min before being slowly withdrawn. 2 weeks after virus inoculation (postoperative day 14), MSCs-derived exosomes were slowly injected into the ventricle (-0.3 mm posterior to bregma, ± 1 mm lateral to midline, and –3 mm ventral to the brain surface) using a stainless steel (26-gauge) injection needle connected to a 1 ml microsyringe (Hamilton). Animals were sacrificed 4 weeks after MSCs-derived exosomes injection.

6. Western blotting

An equal amount of total protein was separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and then transferred to hydrophobic polyvinylidene difluoride (PVDF) membranes (GE Healthcare). The membranes were blocked in 5% skim milk in PBST. Membranes were probed with the following primary antibodies: rabbit anti-αSyn (ab-138501), mouse anti-actin (Santa Cruz, sc-47778), rabbit anti-LC3B (MilliporeSigma, L7543) were used. After overnight incubation at 4℃ with primary antibodies, membranes were incubated with appropriate secondary antibody conjugated to horse radish peroxidase for 2hr at room temperature. Antigen-antibody complexes were visualized with ECL solution (GenDEPOT), For quantitative analysis, immunoblotting band densities were measured by Image J.

7. Quantitative real-time PCR

Total RNA was isolated from SH-SY5Y cells using Trizol reagent (Lugen Sci) according to manufacturer's instructions. An equal amount of RNA (approximately 1 ug) in each experiment was reverse transcribed using an cDNA synthesis premix (Applied Biosystems).

A master mix of the following reaction components was prepared to the indicated end-concentration: 12.5 μl of 2X SYBR green buffer, 2 μl of forward and reverse primer (10 pmol), and 2 μl DNA template (100 ng). Amplification conditions were as follows: initial denaturation at 95℃ for 2min, followed by 40 amplification cycles of 95℃ for 15s and 60℃ for 1 min to anneal and extend, respectively. Quantitative PCR experiments were performed using Applied Biosystems (Thermofisher Scientific). The quantitative real-time PCR reaction was performed using 10pmol each of the primers for human-α-syn and GAPDH (Table 1).

8. Statistical analysis

After verification of normality distribution, mean differences between experimental groups were determined by one-way analysis of variance (ANOVA) followed by a Bonferroni post-hoc test. Differences were considered statistically significant at $p < 0.05$. Statistical analysis was performed using the software SPSS v. 25 (Yonsei University).

Table 1. The primers used for PCR

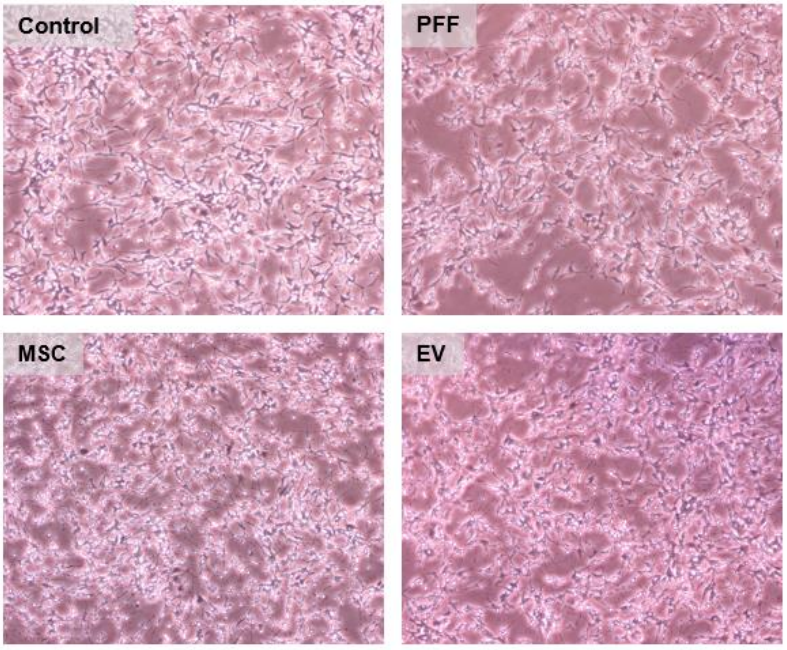
Primer name	Sequence
h-α-syn-F	5′-TTG TGG CTG CTG CTG AGA AA -3′
h-α-syn-R	5′-TCT TCT CAG CCA CTG TTG CC-3′
GAPDH-F	5′-AGT GCC AGC CTC GTC TCA TA-3′
GAPDH-R	5′-GGG TTT CCC GTT GAT GAC CA-3′

III. RESULTS

1. MSCs-derived exosomes treatment increases cell viability and reduces alpha-synuclein in SH-SY5Y cells

To evaluate the effect of MSCs-derived exosomes on the viability and degradation of a αSyn, SH-SY5Y cells were treated with αSyn fibrils for 24 hours. Then, PFF was washed out and cells were cocultured with MSCs or treated with MSCs-derived exosomes for 24 and 48 hours. As expected, PFF treatment decreased cellular viability, whereas treatment with MSCs or MSCs-derived exosomes for 24 hours led to significant increase in cell survival (Figure 1A). Western blot analysis demonstrated that treatment with MSCs or MSCs-derived exosomes for 48 hours attenuates αSyn expression compared to cells treated with only PFF (Figure 1B). The expression of αSyn tended to be decreased in MSC-treated cells compared to MSCs-derived exosome treatment.

A



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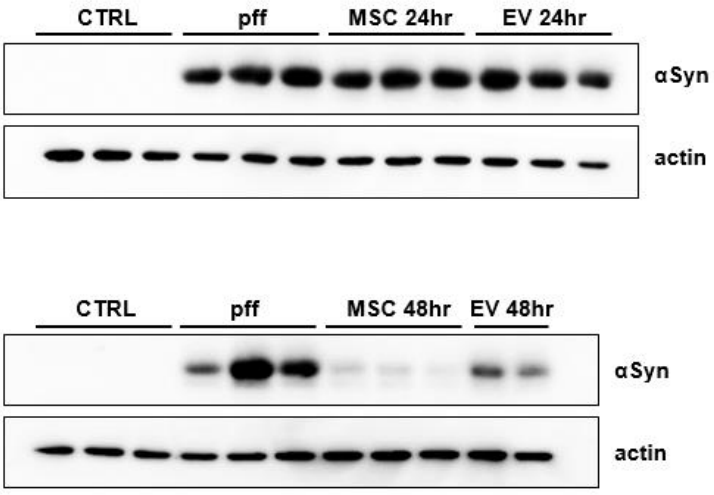

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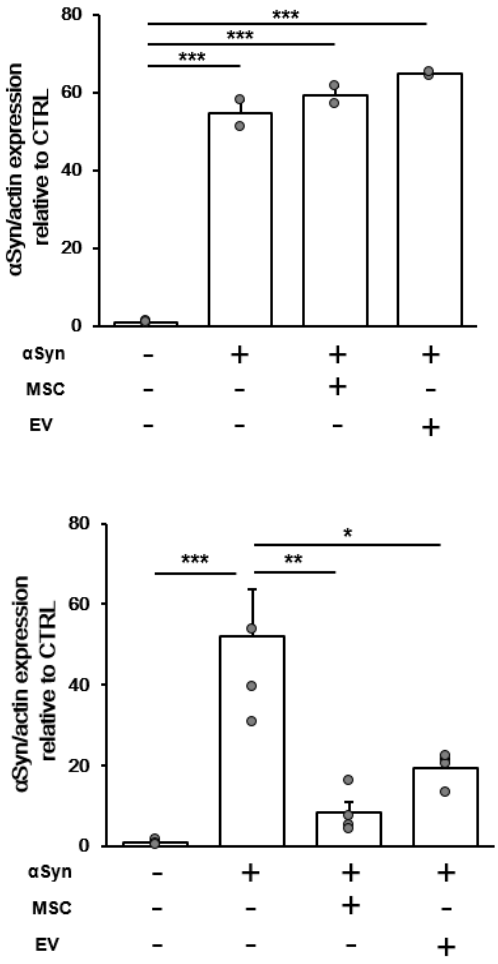
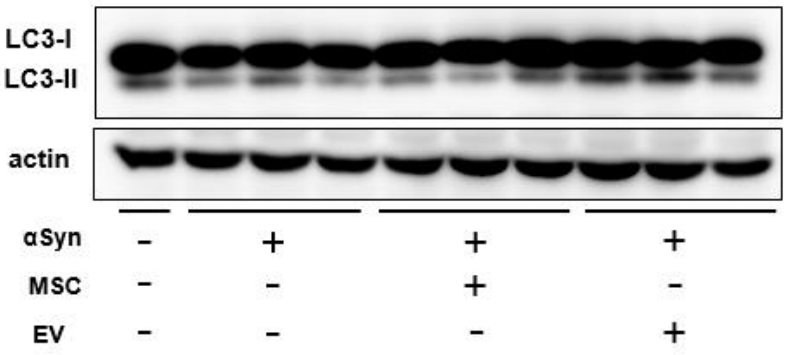


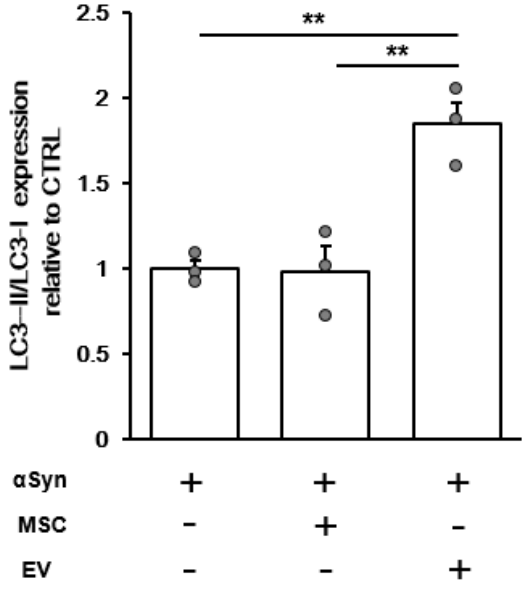
Figure 1. MSCs derived exosomes treatment increases cell viability and reduces alpha synuclein in neuronal cells. (A) cell morphology and viability (B) Western blot for αSyn in control, PFF, co-culture with MSCs group, treatment with MSCs-derived exosomes group (n = 3 per group). (C) Quantification graph of αSyn western blot analysis. Differences among the conditions were evaluated by ANOVA with a Bonferroni correction for multiple comparison. The data are presented as the mean ± SE. *$p<0.05$, **$p<0.01$ and ***$p<0.001$

2. MSCs-derived exosomes enhance autophagolysosome formation in PFF-treated SH-SY5Y cells

To examine the modulatory effects of MSCs-derived exosomes on the autophagic activity in PFF-treated SH-SY5Y cells, we evaluated the expression of autophagy markers. Western blotting showed that the ration of LC3-II/LC3-I, known as a standard marker for autophagosomes was significantly increased in neuronal cells treated with MSCs-derived exosomes relative to PFF-treated cells or MSCs-treated cells (Fig 2A). In addition, the expression of LAMP2 (lysosome-associated membrane protein) was increased in neuronal cells treated with MSCs-derived exosomes compared to PFF-treated cells or MSCs-treated cells (Fig 2B).

A





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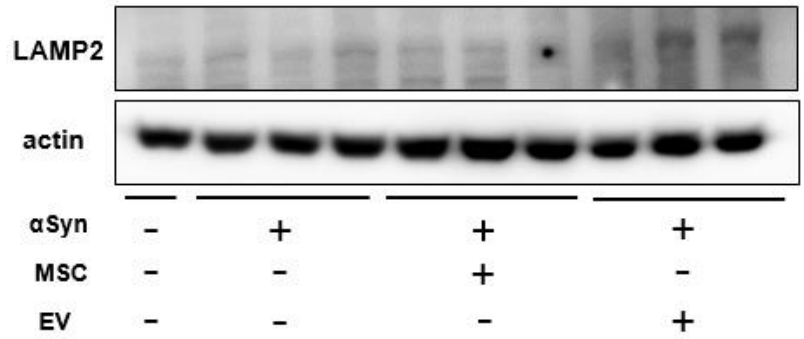

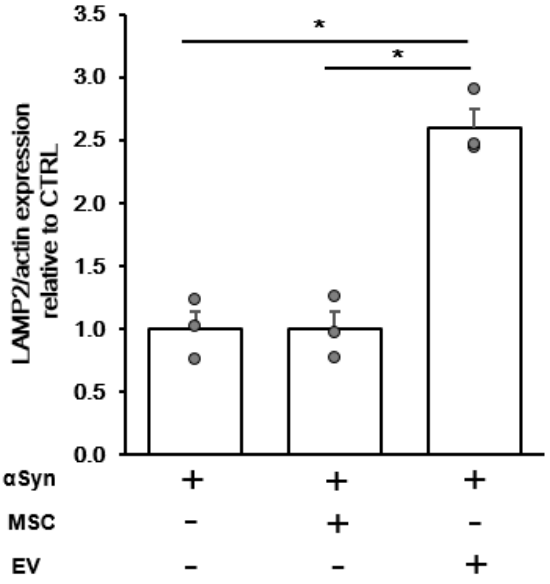

Figure 2. MSCs-derived exosomes increase lysosome activity and enhance autophagy induction in PFF treated SH-SY5Y cells. (A) Western blot for LC3 in control, PFF-treated, MSCs-treated, MSCs-derived exosomes treated neuronal cells and quantification graph (n=1 for CTRL group, n=3 for PFF and MSCs, MSCs-derived exosomes group). (B) Western blot for LAMP2 in control, PFF-treated, MSCs-treated, MSCs-derived exosomes treated neuronal cells and quantification graph (n=1 for CTRL group, n=3 for PFF and MSCs, MSCs-derived exosomes group). Differences among the conditions were evaluated by ANOVA with a Bonferroni correction for multiple comparison. The data are presented as the mean ± SE. *$p<0.05$, **$p<0.01$ and ***$p<0.001$

3. MSCs-derived exosomes reduce α-synuclein in the AAV-αSyn-induced parkinsonian animal models

To examine the effect of MSCs-derived exosomes on αSyn reduction in parkinsonian animal models, we used adeno-associated viral vectors encoding the human wild type α-synuclein (AAV-α-Syn). The virus was directly injected into the SN of mice, which was followed by injection of MSCs-derived exosomes. The *in vivo* experimental design is illustrated (Figure 3A). Western blot demonstrated that the expression of αSyn in the midbrain was significanlty decreased in the mice treated with MSCs-derived exosomes compared to the AAV-α-Syn group (Figure 3B). The expression of dopaminergic neurons in the midbrain tended to be increased in the mice treated with MSCs-derived exosomes compared to the AAV-α-Syn group (Figure 3C).

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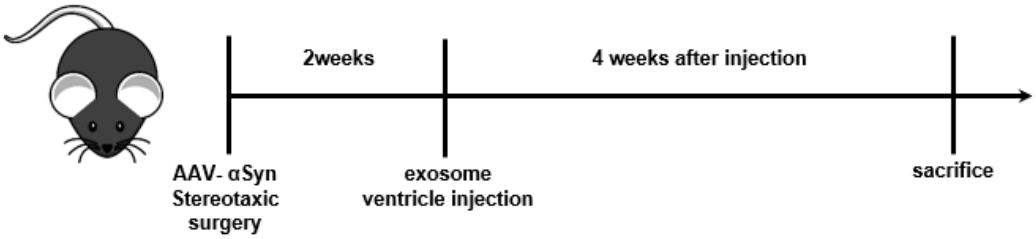

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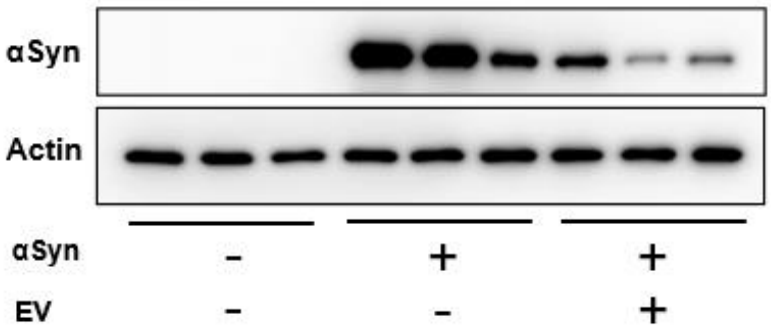

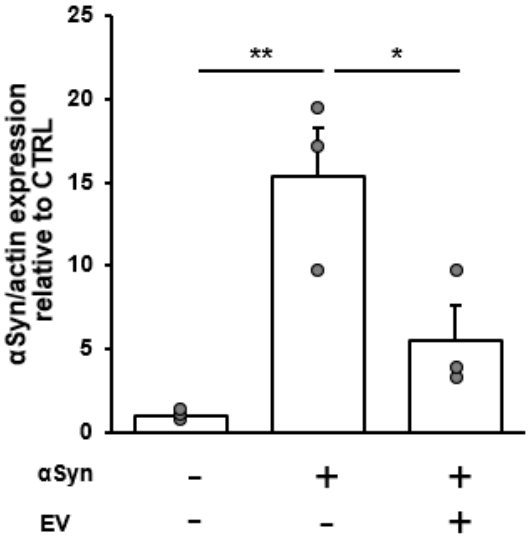

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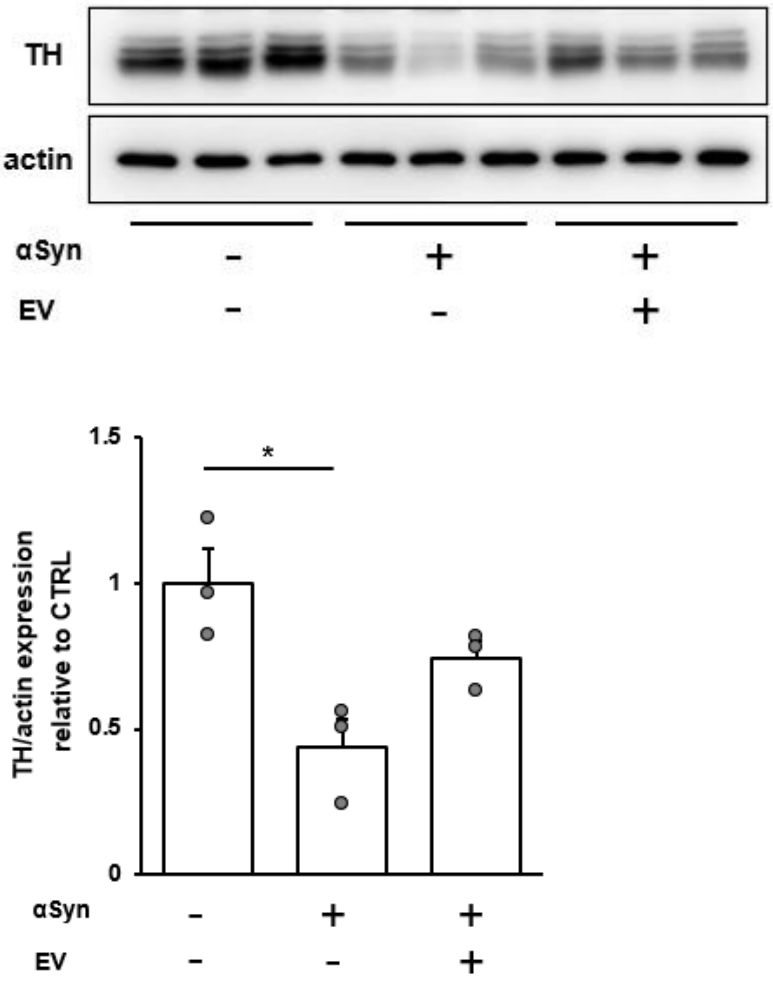
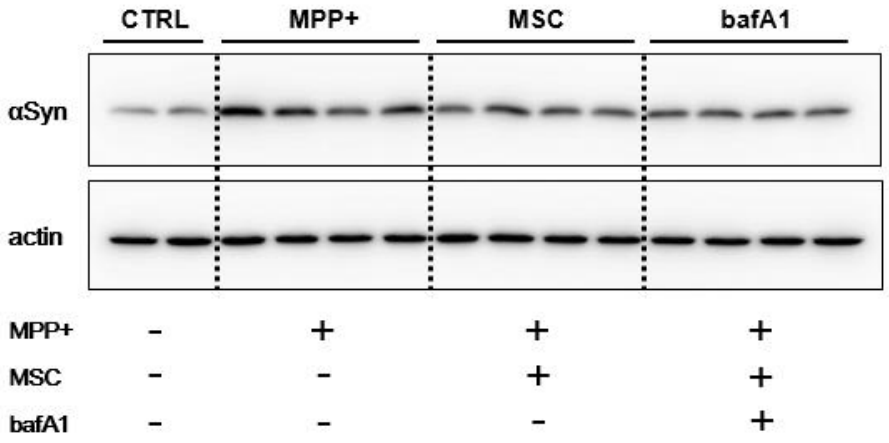


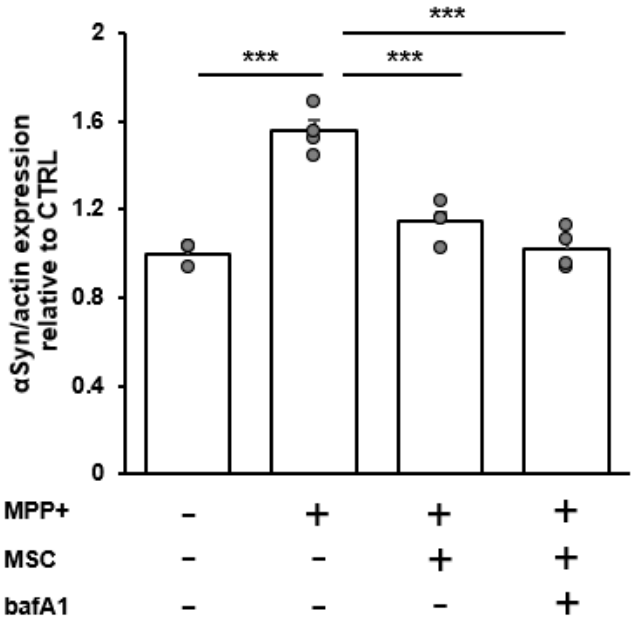
Figure 3. MSCs-derived exosomes reduce α-synuclein levels in AAV- αSyn-induced animal models of PD. (A) Schematic illustrations and schedule design of *in vivo* experiment. (B) Western blot for αSyn in the control, AAV-αSyn virus, MSCs-derived exosomes-treated groups and quantification graph. (n = 3 per group). (C) Western blot for TH in the control, AAV-αSyn virus, MSCs-derived exosomes-treated groups and quantification graph. (n = 3 per group). Differences among the conditions were evaluated by ANOVA with a Bonferroni correction for multiple comparison. The data are presented as the mean ± SE. *p<0.05, **p<0.01 and ***p<0.001

4. MSCs modulate αSyn expression levels in MPP^+-treated SH-SY5Y cells

We examined whether MSCs modulate the levels of αSyn expression in MPP^+-treated SH-SY5Y cells. In a cellular model, western blotting showed that MPP^+ treatment for 48 hours on neuronal SH-SY5Y cells led to an increase in α-synuclein expression and decrease in cellular survival. However, co-culture of MPP^+-treated cells with MSCs increased cellular viability and significantly downregulated αSyn expression (Figure 4A). PCR analysis also showed that MSCs regualted αSyn expression at the transcriptional level in MPP^+-treated cells (Figure 4B). To exclude effect of autophagic clearance, we used a lysosomal inhibitor, Bafilomycin A1. Even after treatment of Bafilomycin A1, the level of αSyn expression was reduced in the MSC co-culture group, suggesting modulating effect of MSCs on αSyn expression would not be mediated by autophagic clearance.

A





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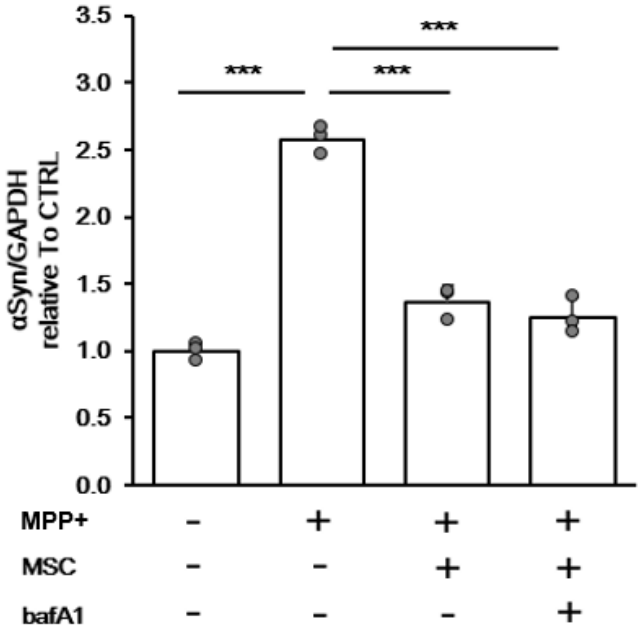
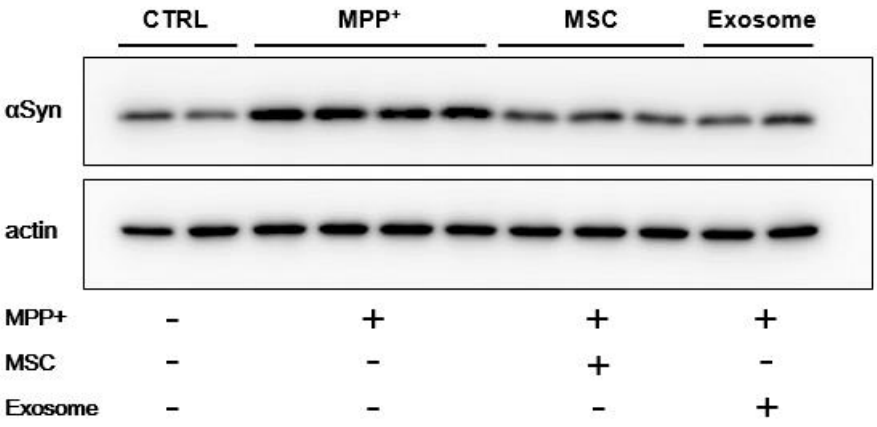


Figure 4. MSCs downregulate α-Syn expression levels in MPP^+-treated neuronal cells. (A) Western blot for αSyn in the control, MPP^+, MSC coculture, MSC coculture with Bafilomycin A1 treated groups and quantification graph (n = 3 per group). (B) Quantitative realtime PCR of αSyn in the control, MPP^+, MSC coculture groups. Differences among the conditions were evaluated by ANOVA with a Bonferroni correction for multiple comparison. The data are presented as the mean ± SE. **$p<0.01$ and ***$p<0.001$

5. MSCs-derived exosomes have property of modulating αSyn expression levels in MPP^+-treated SH-SY5Y cells

To examine whether MSCs-derived exosomes play a pivotal role in modulating αSyn expression levels, MPP^+-treated neuronal cells were co-treated with exosomes isolated from MSCs for 48 hours. Western blot showed that treatment of MSCs-derived exosomes led to reduction in αSyn expression in neuronal cells, similar to the MSCs treatment group. (Figure A)

A



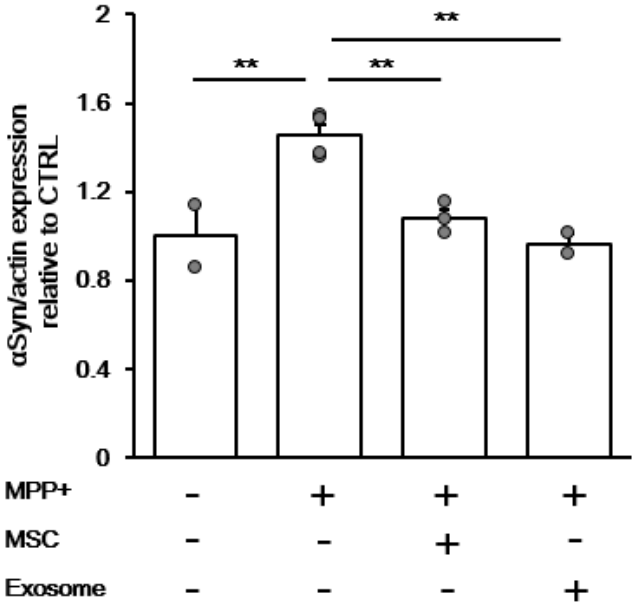


Figure 5. MSCs-derived exosomes downregulate α-Syn expression levels in MPP^+**-treated neuronal cells.** (A) Western blot for αSyn in the control, MPP^+, MSCs co-culture, MSCs-derived exosomes treated groups and quantification graph. Differences among the conditions were evaluated by ANOVA with a Bonferroni correction for multiple comparison. The data are presented as the mean ± SE. **p<0.01 and ***p<0.001

IV. DISCUSSION

The present study investigated whether the treatment of MSCs-derived exosomes can induce autophagic clearance of αSyn and MSCs treatment can modulate expression of αSyn in PD models. The major findings are as follows: (1) MSCs-derived exosomes reduced αSyn by enhancing autophagy mechanism. (2) MSCs have the potential to modulate expression of αSyn at the transcriptional level. Our data suggest that the property of MSCs and MSCs-derived exosomes in modulating αSyn may lead to increased neuronal survival and have a significant therapeutic effect on future PD treatment strategies.

It is well established that αSyn plays a causative role in PD pathology and is one of the most compelling therapeutic targets for Parkinson's disease. Even though the levels of αSyn protein or mRNA is not consistently reported in the brain of patients with PD[24-26], multiplication, mutation, and single nucleotide polymorphisms of SNCA gene, encoding αSyn protein, either can lead to the develepment of PD or cause risk for PD[27-31]. Therefore, reduction of αSyn production may be an important target for disease-modifying therapeutic strategy in PD. Tracy et al. reported that treatment with αSyn antisense oligonucleotides leads to removal of αSyn pathology and reduce dopaminergic cell dysfunction via inhibiting of αSyn production.[27] Doxakis et al. suggested that an increase of miRNA-153 suppressed the expression of αSyn at the mRNA and protein level, which led to neuroprotective effects over dopaminergic cell type.[32-34]

Autophagy is a major intracellular degradation system that delivers cytoplasmic components and structures to the lysosome. It eliminates aggregated protein, cellular debris, damaged organelles and plays a key role in the maintenance of cellular homeostasis[35,36].There are three types of autophagy composed of chaperone-mediated autophagy, microautophagy, and macroautophagy. Among the three forms of autophagy, macroautophagy has known as a major intracellular degradation mechanism. Recent studies have revealed that autophagy is essential for clearance of abnormal αSyn aggregates

and autophagy dysfunction may contribute to neurodegenerative diseases, including PD. Dehay et al. reported the accumulation of autophagosomes was observed in the brains of Parkinson's disease patients and lysosomal dysfunction led to loss of dopaminergic neurons.[37] Esteves et al. reported that lower levels of LAMP2, a marker for the lysosomes was observed in the brain samples of PD patients. [38] Also, McNeil et al. demonstrated that reduction in αSyn level was accompanied by increase in LAMP-1 levels, suggesting correlation between clearance of αSyn and LAMP-1 levels[39]. Therefore, autophagy systems may play pivotal role for inhibiting accumulation of αSyn and eventual neurodegeneration and regulation of autophagy might be a therapeutic strategy for PD.[40] On this basis, Zhao et al. demonstrated that autophagy-regulating miRNAs diminishes the levels of αSyn and alleviate the locomotory impairment of MPTP-treated mice.[41] Furthermore, our previous studies have revealed that MSCs reduce expression of αSyn and lead to neuroprotective effects by modulating autophagy in parkinsonian models.[42]

Consequently, we found that MSCs-derived exosomes significantly decreased expression of αSyn accumulated in cell and increased cellular viability in αSyn-enriched models. In cellular models, MSCs-derived exosomes increased αSyn clearance by enhanced autophagolysosome formation, which led to pro-survival effect on neuronal cells. Western blot in the present study showed that MSCs-derived exosomes treatment led to increased induction of autophagosomes and increased fusion of autophagosomes (LC3-II) with lysosomes (LAMP2), suggesting that MSC-derived exosomes treatment in αsyn fibril-treated neuronal cells increases the process of autophagolysosome formation. These data showed that the effects of exosomes seem to be potent as MSCs, suggesting that they have potential as alternative treatments in PD. Consistent with in vitro data, in vivo study showed that injection of MSCs-derived exosomes significantly decreased expression of αSyn in the regions of the SN in αSyn-inoculated animal models.

After evaluating the autophagy effect in MSCs-derived exosomes, we investigated whether MSCs-derived exosomes also have ability to regulate expression of αSyn. First, we evaluated whether MSCs have effect on modulating expression of αSyn in MPP^+ treated

neuronal cells. Western blot analysis showed that MSCs increased cellular viability and downregulate αSyn expression comopared to the MPP^+ only group. PCR analysis also showed that MSCs regualte αSyn level in transcriptional stage. To demonstrate that these effects are not mediated by autophagy mechanism, we used a lysosomal inhibitor, Bafilomycin A1. Even after treatment of Baf A1, a continued reduction of αSyn was observed in the MSC co-culture group, possibly suggesting direct role of MSCs in the expression of αSyn. Next, we evaluated whether MSCs-derived exosomes play a central role in modulating αSyn expression level in MPP^+ treated neuronal cells. Treatment with exosomes isolated from MSCs for 48 hours led to reduction in αSyn expression in neuronal cells, similar to the MSC treatment group.

In summary, our findings demonstrated that MSCs-derived exosomes increase αSyn degradation via enhancement of autophagy flux and have the ability to modulate αSyn expression in neurotoxin-treated PD models. Accordingly, the present study suggests that the beneficial property of MSCs-derived exosomes on a αSyn modulation might be a therapeutic strategy for PD.

V. CONCLUSION

In conclusion, the present study demonstrated that MSCs-derived exosomes treatment improves αSyn degradation by enhancing autophagy, leading to neuroprotective effect and have the potential to modulate αsyn expression in PD model. This study suggests MSCs-derived exosomes will have a significant therapeutic effect on future PD treatment strategies.

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ABSTRACT(IN KOREAN)

파킨슨 질환에서 중간엽 줄기세포 유래 엑소좀을 통한 자식작용 및 알파 시누클레인 발현 조절 효과 규명

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김이슬

파킨슨병(Parkinson's disease, PD)은 중뇌의 흑질 부위에서 도파민성 신경세포의 선택적 사멸과 루이소체의 발현이 특징인 만성 퇴행성 뇌질환으로서 떨림, 강직, 서동 등의 운동장애가 동반되는 질병이다. 루이소체는 주로 알파시누클레인으로 구성되어 있으며 이러한 알파시누클레인의 비정상적인 발현이나 축적은 파킨슨병의 병인과 밀접한 관련이 있다고 알려져 있다. 따라서 자가포식작용을 증진시킴으로써 알파시누클레인의 축적을 억제하는 것과 전사 단계에서 알파시누클레인의 발현을 조절하는 것은 파킨슨병에 있어 치료적인 전략이 될 수 있을 것으로 보여진다. 본 연구에서 치료제 후보로 제시한 중간엽 줄기세포 유래 엑소좀은 기존 세포의 치료적 이점은 유지하되 세포이식으로부터 발생할 수 있는 다양한 위험성을 피할 수 있기에 줄기세포 기반 새로운 치료제로서 대두되어 왔다. 본 연구에서는, 중간엽 줄기세포 유래 엑소좀이 자식작용을 증강시킴으로써 알파시누클레인을 제거하고, 알파시누클레인의 발현 조절을 유도한다는 것을 규명하여 새로운 치료 전략으로서의 가능성을 제시하고자 한다.

핵심되는 말 : 파킨슨병, 알파시누클레인, 자가포식, 중간엽 줄기세포, 엑소좀

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