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MESENCHYMAL STEM CELLS RESCUE THE ALZHEIMER'S DISEASE CELL MODEL FROM CELL DEATH INDUCED BY MISFOLDED TRUNCATED TAU

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Abstract—We have developed a stably transfected human cell model for Alzheimer's disease with doxycycline-inducible expression of human misfolded truncated tau protein (AT tau). We have showed that AT tau reduced the metabolic activity of the AT tau cells, slowed down cell proliferation, and induced caspase-3–independent apoptosis-like programmed cell death, tauoptosis. The aim of this study was to test the possible capability of rat mesenchymal stem cells (MSCs) to interfere with AT tau protein-induced cell death. AT tau cells after treatment with 10 μM all-trans retinoic acid were either co-cultivated with MSCs or supplemented with MSC secretome for 6 and 9 days. We found that both MSCs and MSC secretome promoted survival and increased the metabolic activity of the cells. Moreover stem cells induced cell differentiation and formation of neurites with numerous varicosities. Strikingly, treatment had no effect on tau expression suggesting that MSC induced self-protecting mechanism that prevented AT tau cells from tauoptosis. Our results showed that mesenchymal stem cells and their secretome are able to rescue the Alzheimer's disease cell model from cell death induced by misfolded truncated tau. We suggest that cell therapy may represent an alternative therapeutic avenue for treatment of human Alzheimer's disease and related tauopathies.

Key words: mesenchymal stem cells, Alzheimer's disease, truncated tau protein.

Mesenchymal stem cells (MSCs), isolated from adult bone marrow, are multipotent and could be used for cell regenerative or cell replacement therapy (Caplan, 1991; Prockop, 1997). They are easily isolated through bone marrow aspiration from donors without serious ethical or technical problems. Furthermore, MSCs can be simply cultivated *in vitro* as plastic adherent cells (Prockop, 1997) to provide a sufficient number of cells for transplantation (Dezawa, 2006). Another important property of MSC is their ability to form colonies *in vitro* after low density plating or single-cell sorting. Single cell-derived colonies of MSC are heterogeneous, with individual cells capable of varying differentiation potential and expansion capacity (Colter et al., 2001; Javazon et al., 2001; Bianco et al., 2008).

Recently, the concept of stem cell therapy has gained a strong foothold in the research of human neurodegenerative disorders (Schwarz and Schwarz, 2010). The principle of cell therapy is based on the restoration of the function lost by the replacement of dead or damaged cells with new healthy ones (Lindvall and Björklund, 2004). Several independent studies performed over the last three decades have shown that neuronal replacement and partial reconstruction of neuronal circuitry have become more feasible. It is important to stress that neural transplantation could be useful mainly for those neuronal subpopulations that have relatively non-specific modulatory actions and whose function does not depend on complex and precisely patterned connectivity (Lindvall and Björklund, 2004). However in Alzheimer's disease, most vulnerable cells developing neurofibrillary pathology belong to the class of glutamatergic pyramidal (projection) neurons that are involved in the corticocortical circuits (Braak and Braak, 1991; Braak et al., 2006). Most likely this was one of the strongest arguments against the application of stem cell therapy in Alzheimer's disease. On the other side mesenchymal stem cells possess unique neuroregenerative and immunomodulatory capacity that may promote neuronal regeneration and regulate neuroinflammation (Joyce et al., 2010; Kassis et al., 2010).

Neurofibrillary pathology, which is the major pathological hallmark of Alzheimer's disease, is composed of hyperphosphorylated tau (Grundke-Iqbal et al., 1986b; Wischik et al., 1988a,b; Lee et al., 1991) and truncated misordered forms of tau protein (Novak et al., 1991, 1993). Previously, we have identified truncated tau species derived from Alzheimer's disease that were conformationally different from normal healthy tau. To validate pathological activity *in vivo*, we expressed the most active form of human truncated tau protein (tau151-391, 4R) as transgene, in the rat brain. Transgenic rats expressing truncated tau displayed massive neurofibrillary degeneration of Alzheimer's type in different brain areas (Zilka et al., 2006). We used the same truncated form of protein tau for the generation of the cell model for Alzheimer's disease

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Abbreviations: AB, alamar blue; AD, Alzheimer's disease; AT tau, human misfolded truncated tau protein; BDNF, brain-derived neurotrophic factor; MSCs, mesenchymal stem cells; RA, retinoic acid.

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(AD). We showed that truncated tau induced specific caspase-3–independent apoptotic-like cell death—tauoptosis (Zilkova et al., 2011). The aim of this study was to test whether mesenchymal stem cells have the potency to prevent the AD cell model from cell death.

EXPERIMENTAL PROCEDURES

Isolation and cultivation of the rat bone marrow-derived stem cells

All experiments were performed in accordance to the Slovak and European Community Guidelines, with the approval of the Institute's Ethical Committee and State Veterinary and Food Administration of the Slovak Republic.

Mesenchymal stem cells were isolated from 6-week-old Wistar male rats. Animals were sacrificed by cervical dislocation and entire femurs were aseptically dissected from hindlimbs and exonerated from the residual muscle and connective tissues. Femurs were removed to 50 ml falcons and transferred to laminar. Epiphysis were cut off under sterile conditions and using sterile technique to avoid cell contamination. Bone marrow was extruded by insertion of a 21-gauge needle attached to a 10-ml syringe through diaphysis and flushed out with 10 ml of basic minimum essential medium alpha (MEM Alpha) (Invitrogen, Carlsbad, CA, USA). Strong flushing was necessary during the marrow cell preparation. Flushed cells were collected into a 10-ml tube situated under plug out of the cut end of the bone and centrifuged for 10 min at 1200 rpm at room temperature. Supernatant was removed, cells were resuspended in 10 ml of culture medium—MEM Alpha (Invitrogen), 15% FBS (Invitrogen), 10 U/ml gentamycin (PAA Laboratories GmbH, Paching, Austria), 2 mM L-glutamine (PAA Laboratories GmbH), and counted in Bürker chamber. Typically, we obtain 1×10^8 BM cells from one donor. The cells were plated at density 6×10^6/60 cm^2 and incubated at 37 °C in humid air with 5% CO_2. After 24–48 h, non-adherent cells were removed by changing the medium. Cells were cultured for 1 month and medium was changed every 3–4 days.

Flow cytometry

For flow cytometric analysis, cells were detached with accutase (PAA Laboratories GmbH, Pasching, Austria) and sequentially stained with FITC-conjugated primary antibodies anti-CD90 (AbD Serotec, Kidlington, UK), anti-CD44 (BD Biosciences Pharmingen, NJ, USA), and CD11b (AbD Serotec, Kidlington, UK) at a concentration of 2 μg/ml at 4 °C for 30 min. The stained cells were analyzed using FACS Callibur flow cytometer (BD Biosciences Pharmingen, NJ, USA). Win MDI 2.8 software was used to create histograms. Classification criteria were as follows: $<$10%, no expression; 11–40%, low expression; 40–70%, moderate expression; $>$70%, high expression.

Analysis of the neurotrophin expression by ELISA

MSCs (31,250 cells/cm^2) at varying passages were cultured for 24 h in serum-free α-MEM and then aliquots (50 μl) of the culture supernatant were analyzed by the $E_{max.}$ ImmunoAssay System BDNF, β-NGF, and GDNF immunoassays (Promega, Madison, USA) according to the manufacturer's instructions. All samples were analyzed in triplicate.

Alzheimer's disease cell model expressing human misfolded truncated tau (AT tau cells). Development of the double-stable transfected SH-SY5Y cells were described previously (Zilkova et al., 2011). Briefly, SH-SY5Y neuroblastoma cells were used for generation of the cell model system according to manual (BD Biosciences Clontech, USA). The procedure includes two sequential transfection steps, which were performed by FuGENE 6 (Roche Diagnostics GmbH, Germany). First round of transfection was done by regulator plasmid pTet-Off, which encodes the tetracycline-controlled transactivator (tTA) and also includes a neomycin-resistance gene to permit selection of stably transfected cells. The second round of transfection was performed as a co-transfection of the response plasmids pTRE2 (tau151-391, 4R) or pTRE2 (tau40, 4R) under the control of the tetracycline-response element (TRE) together with additional response vector pTKHyg (Tet-Off regulator system, BD Biosciences Clontech, USA). After selection of the clones using antibiotics G418 and hygromycin, we isolated cell colonies and screened for the expression of the tau 151-391. The AT tau cells were maintained in basal medium containing minimum essential medium and Ham's F12 medium (PAA Laboratories GmbH) (1:1) with 10% fetal bovine serum (Invitrogen), 2 mM L-glutamine (PAA Laboratories), 1% non-essential AA (PAA Laboratories), 50 μg/ml gentamycin (PAA Laboratories). The basal medium was supplemented with, and 50 μg/ml G418 (Invitrogen), 100 μg/ml hygromycin B (Invitrogen), and 10 ng/ml doxycycline (Sigma-Aldrich, St. Louis, MO, USA). Tau expression was induced by cultivation of cells in medium without doxycycline.

Experimental design

Two independent experimental approaches were proposed. The first one consisted of neuroblastoma cells expressing truncated tau151-391 (AT tau cells) and MSC co-cultures (Fig. 1A). AT tau cells were cultivated in basal medium without doxycycline (Sigma-Aldrich) for AT tau induction and supplemented with 10 μM all-trans retinoic acid for 5 days. Then the cells were plated into 12-well plates in plating density 15,000 cells/cm^2. MSCs were seeded onto polycarbonate inserts with 1 μM pore size in same plating density and cultivated with AT tau cells for 6 and 9 days. The medium was changed every second day. The second approach was based on the AT tau cells cultivated in the same conditions as shown above (Fig. 1B). Instead of MSCs, the medium enriched with secretory products of MSCs (secretome) was used.

Isolation of total tau from cultivated cells

Cells were harvested and homogenized in TTL lysis buffer (20 mM Tris, pH 7.4; 150 mM NaCl, 1 mM EDTA, 1 mM DTT, 1 mM Na_3VO_4, 20 mM NaF; 0.5% Triton X-100) containing protease inhibitor cocktail Complete, EDTA-free (Roche Diagnostics, Indianapolis, IN, USA). The homogenate was snap-frozen in liquid nitrogen and thawed in ice to complete the cell lysis. Clear cell extracts were obtained by centrifugation at 20,000$\times$g for 10 min at 4 °C. Protein extractions from cells were performed at sixth and ninth day after MSC therapy procedure.

Western blot analysis

Protein concentrations of cell lysates were determined by Bradford Bio-Rad protein assay (BioRad Laboratories GmbH, Munich, Germany). Ten micrograms of total protein was separated by electrophoresis in 12% sodium dodecylsulphate (SDS)–polyacrylamide gels and then transferred to nitrocellulose membrane (Schleicher & Schuell, Dassel, Germany) in 10 mM N-cyclohexyl-3-aminopropanesulfonic acid (CAPS, pH 11; Roth, Germany). After transfer the membranes were stained with Ponceau S to verify the uniform transfer of the proteins. Membranes were blocked in non-fat milk (5% milk in TBS; 0.1% Tween 20) for 1 h. Then they were incubated with cell culture supernatant of hybridoma cells producing pan-tau monoclonal antibody DC25 recognizing residues 347–354 (Axon Neuroscience, Vienna, Austria) overnight at 4 °C, followed by polyclonal goat anti-mouse IgG, horseradish peroxidase-conjugated (1:3000; Dako, Glostrup,

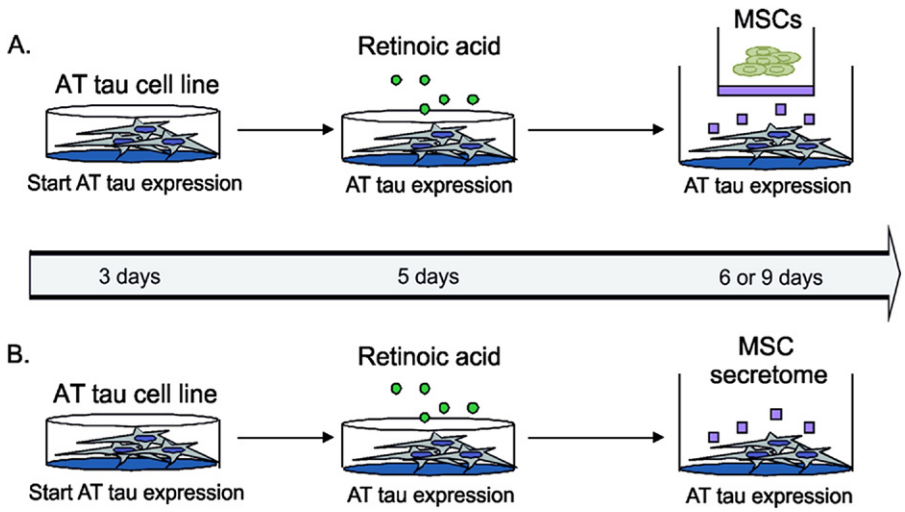

Fig. 1. Experimental design. Two experimental approaches were used. (A) AT tau cells cultivated in basal medium without doxycycline were treated with 10 μM all-trans retinoic acid for 5 d. After RA treatment, the AT tau cells were seeded on the bottom of 12-well plates (lower compartment) and MSCs were plated onto polycarbonate inserts (upper compartment). The co-culture was cultivated for 6 and 9 d. (B) In the second experimental set-up, AT tau cells were cultured in absence of MSCs. The basal cultivation medium was enriched with MSC secretome in ratio 1:1. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

Denmark) for 1 h at RT. Blots were developed using enhanced chemiluminescence Western blotting detection system SuperSignal® West Pico Chemiluminescenscent Substrate (Thermo Scientific, USA) on Image Reader LAS-3000 (Fuji Photo Film Co., Ltd., Tokyo, Japan). Immunoblots were quantified using AIDA Biopackage (Advanced Image Data Analyser software; Raytest, Straubenhardt, Germany).

Metabolic activity analysis

Metabolic activity (viability) of the AT tau cells was measured by alamar blue (AB) fluorescence (AbD Serotec, Oxford, UK). The active ingredient of alamarBlue® (resazurin) is a non-toxic, cell-permeable compound that is blue in color and virtually non-fluorescent. Upon entering cells, resazurin is reduced to resorufin, which produces very bright red fluorescence. Viable and metabolically active cells continuously convert resazurin to resorufin, thereby generating a quantitative measure of metabolic activity and cell viability—cell fitness. ATP levels were evaluated by CellTiter-Glo® Luminescent Cell Viability Assay (Promega, Madison, USA). Resulting AB fluorescence and ATP luminescence was measured using a Fluoroscan Ascent FL (MTX Lab Systems, Inc., USA).

Statistical evaluation

All data sets are expressed as the mean±standard error of the mean (SEM). Results were examined by two-way ANOVA followed by Bonferroni's post hoc test using Prism GraphPad Software Version 4.03 (Graph Pad Software, Inc., USA). To compare two groups Mann–Whitney *U*-test was applied. Differences were considered to be statistically significant if $P<0.05$.

RESULTS

Bone marrow-derived stem cells expressed specific surface markers for progenitor cells

The mesenchymal stem cells were isolated from the rat bone marrow. The initial culture of the isolated MSCs contained a heterogeneous cell population with both round and fibroblastic cells. However, the number of round-shaped cells gradually decreased and the growth rate of the fibroblastic cells gradually increased over time. Generally, the MSCs showed typical fibroblastic morphology (Fig. 2A). The immunophenotype characteristics of the MSCs were analyzed by flow cytometry. The MSCs positively expressed surface markers specific for progenitor cells including thymocyte differentiation antigen 1 (Thy-1, CD90) (Fig. 2B) and receptor for hyaluronic acid (CD44) (Fig. 2C). In contrast, the cells expressed very low levels of the integrin alpha M (CD11b) (Fig. 2D), which is considered to be the characteristic marker of lymphohematopoietic cells. Finally, we measured the levels of several trophic factors according to Crigler et al. (2006). Interestingly, the levels of brain-derived neurotrophic factor, nerve growth factor, glial cell line-derived neurotrophic factor, and neurotrophin-3 were under detection limit of the immunoassays (data not shown).

Mesenchymal stem cells and their secretome rescued AD cell model expressing Alzheimer's truncated tau from cell death

Our previous studies showed that Alzheimer's truncated tau (AT tau) reduced the viability and induced the death of the cellular model for Alzheimer's disease (Zilkova et al., 2011). In this study we have tried to differentiate the AT tau cells using retinoic acid and then reverse the tau-mediated death by using MSC culture. Interestingly, retinoic acid (RA) treatment *per se* did not ameliorate the tau-induced death. The proliferation of AT tau cells rapidly decreased after 6 days of cultivation (Fig. 3).

To neutralize the toxic effect of AT tau, the AT tau cells were co-cultivated with MSCs. Alternatively, we supplemented the AT tau cells medium with MSC secretome. Surprisingly, MSCs or their secretome did not affect the expression levels and the pattern of total AT tau protein

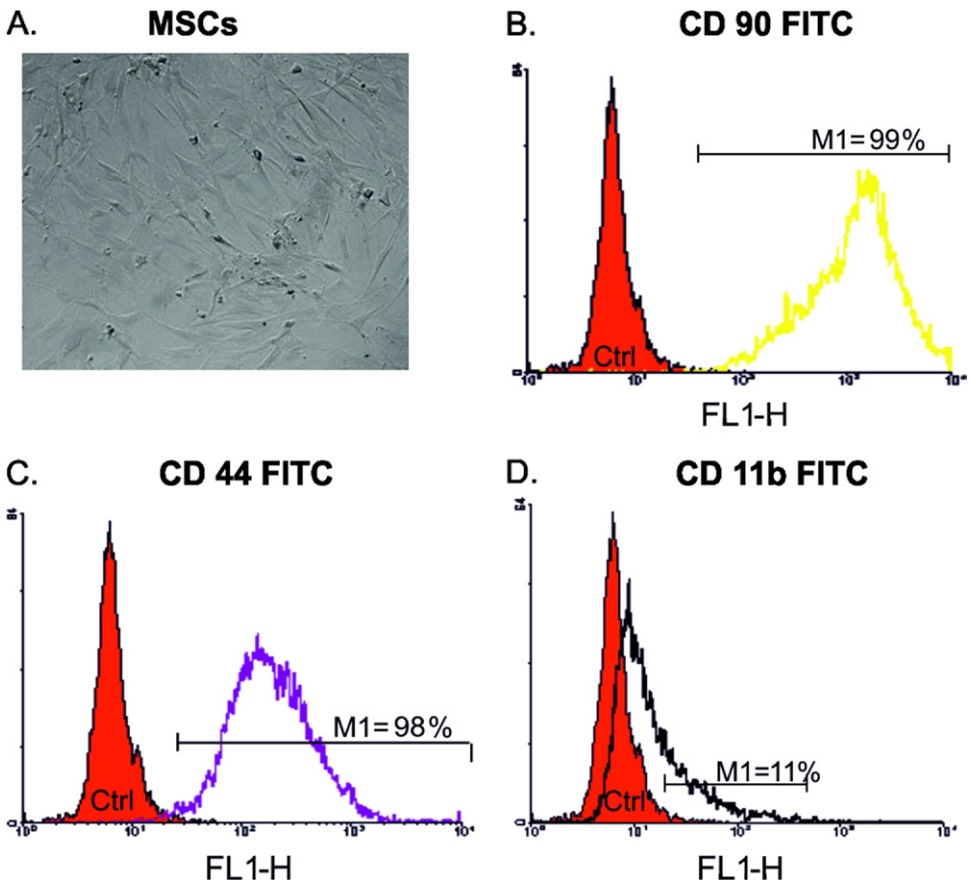

Fig. 2. MSCs morphology and characterization. MSCs maintained homogenous fibroblast-like morphology after 3–4 passages (A). Characterization of the MSCs was done by flow cytometry, which showed expression of surface markers specific for progenitor cells: CD90 (B) and CD44 (C). It is important to note that MSCs were negative for cell surface markers associated with lymphohematopoietic cells—CD11b (D).

(Fig. 4A, B). However, analysis of the cell metabolic activity showed that MSCs or their secretome significantly increased the viability of AT tau cells ($P<0.0001$). The metabolic activity measured by AB showed that MSCs elevated AB fluorescence above 46% and MSC secretome above 77% (Fig. 4C). Moreover, MSCs elevated cellular level of ATP above 69% and MSC secretome above 56% (Fig. 4D). Brain-derived neurotrophic factor (BDNF) treatment promotes cell survival only very slightly. AB fluorescence of the AT tau cells treated with BDNF did not increase significantly (above 8%) in comparison to non-treated AT tau cells. On the other side, metabolic activity measured by ATP level evaluation showed that BDNF treatment significantly increase the cell viability ($P<0.0001$) (Fig. 4C, D); however, this elevation was only 15% above the controls. MSCs or MSC secretome displayed significantly stronger rescue effect than BDNF alone (MSCs vs. BDNF, $P<0.0001$; MSC secretome vs. BDNF alone, $P<0.0001$).

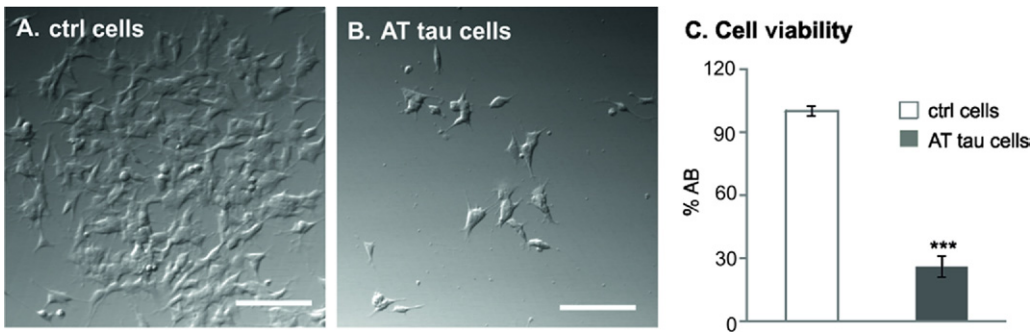

Fig. 3. AT tau cells treated with retinoic acid showed reduced cell viability. Confocal microscopy analysis showed that number of living AT tau cells expressing human truncated tau rapidly decreased after 5-d-long cultivation with 10 μM retinoic acid (B) in comparison to cells without AT tau (A). Metabolic analysis done with alamar blue (AB) assay confirmed significant decrease of cell viability in cells with AT tau expression (*** $P<0.0001$) (C). Tool bar: 50 μm. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

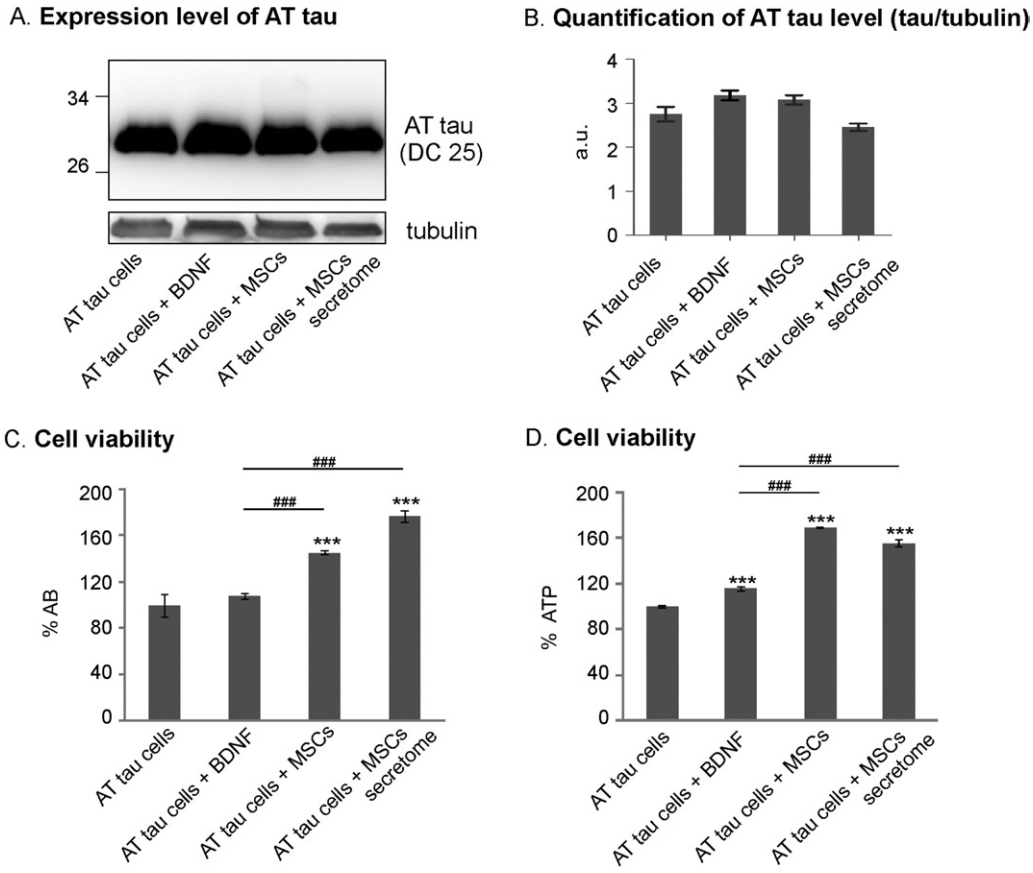

Fig. 4. Mesenchymal stem cells improved viability of AT tau cells viability. The expression levels and the pattern of truncated tau protein remained stable during the MSC treatment. Western blot analysis was done with DC25 and anti-tubulin antibodies (A). Quantification of AT tau level was done by calculation of tau/tubulin. Mean and standard error (SE) are shown (B). Metabolic analysis measured by AB (C) and ATP assay (D) showed that MSCs or its secretome significantly increased the viability of AT tau cells (*** $P<0.0001$). Although BDNF treatment did not significantly increase metabolic activity measured by alamar blue ($P>0.05$), the ATP level was increased significantly after BDNF treatment (*** $P<0.0001$). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

Rescue effect of BMSCs on AT tau cells survival increased in time

MSCs and MSC secretome appeared to promote both survival and proliferation of AT tau cells and this effect increased in time ($P<0.0001$) (Fig. 5). Surprisingly, MSC secretome showed even higher neuroregenerative capacity compared to MSCs after 6- and 9-day-long cultivation. In comparison to MSCs culture, the secretome increased AT tau cell viability by 31% above controls after 6 days and above 81% after 9-day-long cultivation.

Mesenchymal stem cells and their secretome promoted neuritogenesis in AT tau cells

In order to identify whether MSCs or their secretome can promote neuritogenesis in the cells affected by tau-mediated toxicity, we did the microscopy analysis of the AT tau cell morphology. As we expected, AT tau cells were not able to differentiate in the medium supplemented with retinoic acid (Fig. 6A, B). Surprisingly, treatment with 50 ng/ml rhBDNF showed limited number of processes and varicosities (Fig. 6C, D). Contrary to BDNF treatment, both MSCs and MSC secretome markedly changed the morphology of AT tau cells. We found that AT tau cells co-cultivated with MSCs readily differentiated and acquired typical neuronal morphology characterized by the development of multiple neuritic processes and varicosities (Fig. 6E, F). The similar pattern was displayed by AT tau cells treated with MSC secretome (Fig. 6G, H).

DISCUSSION

Tauopathies represent a heterogenous group of human neurodegenerative disorders characterized by aberrant folding of protein tau leading to its intracellular and extracellular accumulation (Grundke-Iqbal et al., 1986a,b; Wischik et al., 1988a,b; Braak and Braak, 1991; Lee et al., 1991; Delacourte et al., 1999; Sergeant et al., 2005). Nowadays it is widely accepted that tau cascade portrays valuable target for prospective therapeutic development of human tauopathies including Alzheimer's disease. Pharmacological research has identified several therapeutic approaches targeting directly or indirectly tau cascade such as inhibition of tau aggregation, prevention of tau hyperphosphorylation, promotion of proteolytic degradation, or vaccine-mediated clearance of misfolded tau

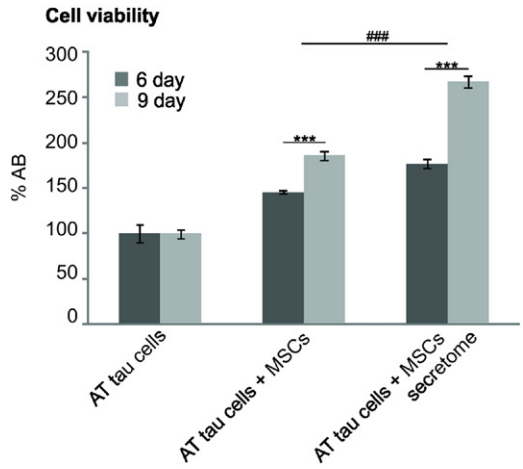

Fig. 5. Therapeutic effect of mesenchymal stem cells increased in time dependent manner. Survival and the proliferation of AT tau cells increased in time after the treatment with MSCs or MSC secretome (*** $P<0.0001$). Interestingly, MSC secretome showed even higher improvement than MSCs (### $P<0.0001$). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

(Dickey and Petrucelli, 2006; Iqbal and Grundke-Iqbal, 2008; Schneider and Mandelkow, 2008; Zilka et al., 2008; Brunden et al., 2009, 2010). Recent developments in stem cell technology raise the prospect of cell therapy for human neurodegenerative tauopathies. Transplantation of the neural stem cells or administration of mesenchymal stem cells isolated either from human umbilical cord or from the bone marrow has produced beneficial effects in several independent animal models of AD and tauopathies (Nikolic et al., 2008; Blurton-Jones et al., 2009; Hampton et al., 2010; Lee et al., 2010, in press). Above-mentioned reports have shown that the neuroprotective effect of stem cells may be mediated (1) by their ability to produce various trophic factors that contribute to functional recovery or (2) by activation of neuroinflammatory pathways. In the present study we showed that bone marrow-derived stem cells can prevent tau-mediated cell death in the Alzheimer's cell model.

Previously, we developed the cellular model for AD expressing misfolded protein tau derived from Alzheimer's disease. The AT tau cells were generated on the background of the neuroblastoma cell line SH-SY5Y, since this line posses many characteristics of adult human neurons. In the previous report, we showed that human truncated tau slowed down the cell proliferation. This phenomenon was revealed by the doubling time extension and additionally confirmed by a reduction in metabolic activity (alamar blue). Moreover, truncated tau induced the increased release of the adenylate kinase from the cells and caused cell shrinkage, nuclear and DNA fragmentation (Zilkova et al., 2011). To modify the cell death induced by truncated tau, we co-cultivated the retinoic acid-treated AT tau cells and rat bone marrow-derived stem cells. It has been shown that the RA treatment stimulated SH-SY5Y cells to adopt a phenotype that is functionally and electrically similar to neurons (Abemayor and Sidell, 1989; Encinas et al., 2000). Simultaneously, RA induced differentiation through regulation of the transcription of neurotrophin receptor genes and the Wnt signaling pathway (Uemura et al., 2003; Clagett-Dame et al., 2006). We found that RA treatment did not ameliorate the cell death-inducing potential of the truncated tau. However, when the AT tau cells were co-cultivated with MSCs, we observed significant improve-

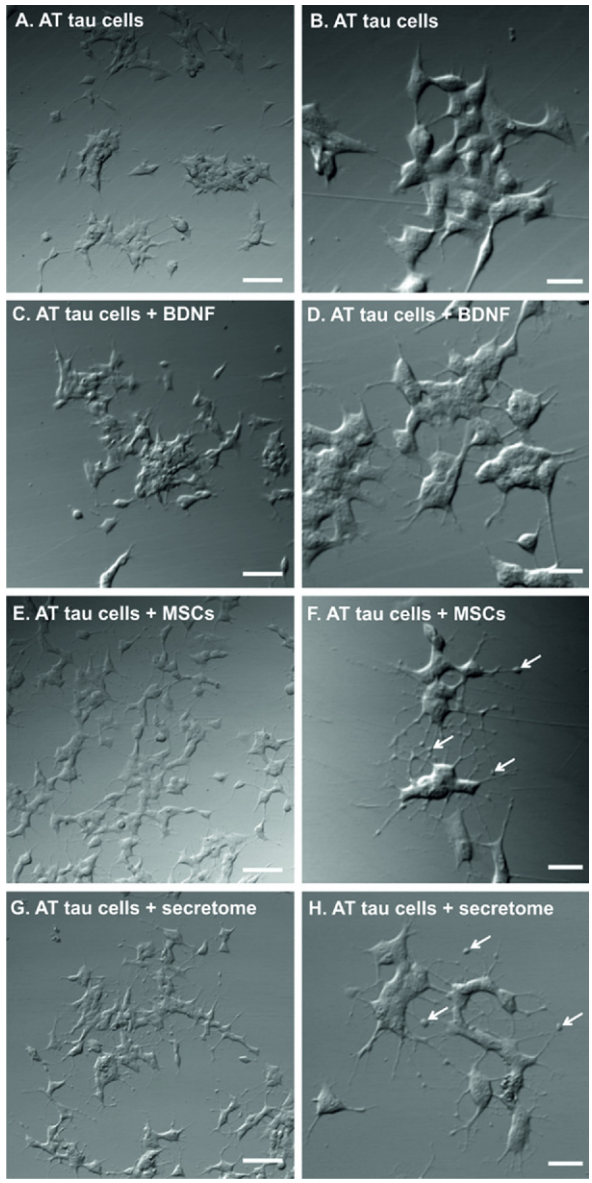

Fig. 6. Mesenchymal stem cells markedly promoted neuritogenesis of the AT tau cells. Confocal microscopy analysis showed that retinoic acid treatment alone did not induced neuritogenesis of the AT tau cells (A, B, high magnification). The RA treatment followed by BDNF led to the development of several small processes (C, D, high magnification). The increased amount of processes and varicosities (arrows) were detected in AT tau cells treated with RA and MSC secretome (G, H, high magnification). Similarly, MSCs induced extensive growth of neuronal processes containing multiple varicosities (E, F, high magnification). Tool bar: 50 μm (A, C, E, G), 20 μm (B, D, F, H). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

ment of the proliferation of AT tau cells. Moreover, the MSC secretome displayed even more robust improvement. Rescue efficacy of the MSC or its secretome increased in time-dependent manner. However, MSC treatment had no effect on tau expression. These findings strongly suggest that the MSCs have the potential to neutralize truncated tau-induced cell death without affecting tau protein degradation.

Several independent studies have indicated that MSC had potency (1) to produce neuroprotective or neurotrophic factors that support neuronal cell survival, (2) to induce endogenous cell proliferation, and (3) to promote the nerve fiber regeneration at sites of injury (Li et al., 2002; Mahmood et al., 2004; Crigler et al., 2006). In this work, we found that treatment with brain-derived neurotrophic factor slightly improved the proliferation of AT tau cells; however, the effect was significantly lower than that of MSCs. It is reasonable to assume that the MSC secretome contains the complex bio-active factors that can protect the neuronal cells from tau-mediated cell death.

One of the most exciting findings of this study is the ability of MSC to promote neurite outgrowth in the cells expressing truncated tau. Interestingly, BDNF treatment did not promote differentiation of AT tau cells to such a degree as did the treatment with MSCs. Previously it has been shown that BDNF expression is not sufficient for the neurite-inducing activity of MSCs (Crigler et al., 2006). It suggests that BDNF after all may not be the crucial player in the therapeutic activity of the MSC secretome. Uncovering the molecular mechanisms that govern therapeutic effect of the MSC remains a great challenge for the future experiments.

CONCLUSIONS

Taken together, these data clearly indicate that mesenchymal stem cells have significant impact on tau cell death cascade and can ameliorate toxic effect of misfolded truncated tau. We suggest that the cell neuroprotective therapy rather than cell replacement therapy represents prospective strategy for treatment of Alzheimer's disease and related tauopathies.

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