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Original Article

Influences of umbilical cord mesenchymal stem cells and their exosomes on tumor cell phenotypes

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Abstract: Mesenchymal stem cells (MSCs), extensively utilized in contemporary stem cell research, hold significant potential in the treatment of neoplastic diseases. This study aims to investigate the influences of umbilical cord mesenchymal stem cells (UMSCs) and their exosomes (UMSCs-exos) on tumor cell phenotypes. UMSCs and UMSCs-exos, isolated from human umbilical cord tissue, were validated for isolation efficiency and differentiation capacity using flow cytometry, electron microscopy, and cell staining. MDA-MB-231, BGC-823, A549, and LN-229, which are human breast (BC), gastric (GC), lung carcinoma (LC) cells and glioma cells, respectively, were treated with UMSCs and UMSCs-exos. Cell counting kit-8 (CCK-8), cell scratch-wound, and Transwell assays were performed on treated cultures to observe the phenotypic changes induced by UMSCs- and UMSCs-exos-treated cancer cells. The results demonstrated that UMSCs highly express PE-labeled positive surface antigens and exhibit low expression of FITC-labeled negative surface antigens, alongside possessing osteogenic and adipogenic differentiation potentials. Electron microscopy revealed UMSCs-exos to be approximately 30-150 nm in diameter, averaging 126.62±1.64 nm, and displaying increased Tsg101, CD9, and CD63 protein expression. Moreover, MDA-MB-231 and BGC-823 cells exhibited enhanced proliferation, invasion, and migration upon UMSCs and UMSCs-exos treatment. In contrast, A549 cells showed minimal alteration to invasiveness but a marked increase in proliferation and migration capabilities, while LN-229 cells displayed a phenotype indicative of suppressed activity. In conclusion, UMSCs and UMSCs-exos effectively promote the growth of BC and LC cells and inhibit the activity of GC and glioma cells, presenting promising avenues for future neoplastic disease treatments.

Keywords: Umbilical cord mesenchymal stem cells, exosomes of umbilical cord mesenchymal stem cells, tumor phenotype, glioma, gastric carcinoma, lung carcinoma

Introduction

Stem cells have emerged as a focal point in contemporary medical research, primarily due to their unique biological characteristics that enable effective treatment of various diseases, including cardiovascular disorders, organ transplantation, organ fibrosis, and skeletal diseases [1-4]. Mesenchymal stem cells (MSCs), one of the most extensively studied stem cells in current stem cell research, originate from the mesoderm in early embryonic development. They are found in nearly all tissues and cellular matrices, exhibiting self-renewal and multidirectional differentiation potentials [5, 6]. As the research progresses, MSCs have been found to exhibit various differentiation effects on fat, bone, cartilage, muscle cells, etc. [7]. In addition to cell differentiation, MSCs also possess immunomodulatory and anti-inflammatory properties, contributing to the burgeoning research on their potential in treating neoplastic diseases [8].

Tumors are known to arise from masses that are formed by uncontrolled normal cell growth with a substantial or diffuse distribution. Commonly, neoplastic diseases can be defined using four characteristics of cell activity: asymptomatic sustained growth and division, cell avoidance of programmed death, promotion of angiogenesis through cell division, and continu-

ous invasion and metastasis of tumor cells. Therefore, the direct approach to treating tumors involves inhibiting tumor cell activity and promoting cell apoptosis [9, 10]. MSCs and their exosomes (exos) have been found to be effective in promoting the dormancy of cancer cells, changing the tumor microenvironment, and inhibiting tumor progression [11, 12].

Umbilical cord (UC) MSCs (UMSCs) have gained increasing attention in stem cell research due to their advantages such as low immunogenicity, easy acquisition from tissues for culture, and lack of ethical controversy [13]. However, the potential interactions of UMSCs, UMSC-exos, and tumor cells remains poorly understood due to a lack of available research. Therefore, this study aims to analyze the influence of UMSCs and UMSC-exos on tumor cell phenotypes, providing foundational data for the future clinical application of UMSCs and guiding new research directions in tumor management.

Materials and methods

UC sample source

The study involved pregnant women with normal full-term pregnancies who delivered at our hospital between January 2021 and October 2021. Following informed consent from the mothers, umbilical cord (UC) tissues and blood were collected post-childbirth and tested for pathogenic microorganisms and viral infections. Research proceeded only after confirming the absence of contamination.

UMSC culture

UC tissues were evenly distributed in a petri dish and immersed in Glucose Dulbecco's Modified Eagle's Medium (LG-DMEM) supplemented with a 20% volume fraction of fetal bovine serum (FBS, Thermo Scientific), 2 mmol/L-Glu (Thermo Fisher Scientific), and 1% volume fraction of penicillin-streptomycin (Life Technologies, USA). Cultures were maintained at 37°C in a 5% CO_2 incubator. Cell morphology was monitored under an inverted microscope. Medium was changed every 2 days when the cells were found to migrate from the periphery of the tissue mass and adhere to the wall. Passage was performed when the cells reached 70-80% confluency. This procedure was repeated, selecting cells at the 5th passage for experimental analysis.

UMSC identification

Cells at the 5th passage were treated with 0.02% ethylene diamine tetraacetic acid (EDTA) upon reaching over 80% confluence. The petri dish was agitated gently to ensure the dissociation solution covered all cell surfaces. Some MSCs were transferred to a 75-cm^2 plastic culture flask. For dissolution of cells out of 75-cm^2 flasks, 5 mL volume fraction 0.2% trypsin/0.2% EDTA (5 mL) was added after removing the culture solution. Cell morphology was observed under the microscope. Digestion was terminated by addition of a digestion termination solution when most cells appeared rounded. Post-centrifugation (10 min at 1000 rpm), the supernatant was discarded, and cells were stained with CD11b, CD34, CD45, CD90, CD73, and CD105 antibodies (BD Pharmingen, San Diego, USA). Flow cytometry was used to determine antigen expression, with data analysis via FlowJo software (Tree Star, Inc., Ashland, Oregon, USA). An unstained control group was used to assess background.

UMSC differentiation capacity detection

Cells at 80-90% confluence were treated with 0.25% trypsin/0.04% EDTA, seeded in 6-well plates at a density of $2 \times 10^4/cm^2$, and cultivated in 2 mL of complete medium. For osteogenic differentiation, cells at 60-70% confluence were treated with osteogenic induction medium (2 mL), changed every three days. After 2-4 weeks, UMSCs were stained with alizarin red S to assess osteogenic differentiation. For adipogenic differentiation, cells at 100% confluence were treated with adipogenic induction medium A for three days, then pulsed with medium B for 24 hours before switching back to medium A. This procedure was repeated 3-5 times. Oil red O staining was used to evaluate adipogenic differentiation.

Isolation of UMSCs-exos

UMSCs were seeded in a cell culture flask and grown to 80-90% confluence for subculture. Fresh culture supernatant of the UMSCs was collected and UMSCs-exos were isolated by differential centrifugation utilizing the isolation kit supplied by Searle, Thermo Fisher Scientific, USA, following the manufacturer's protocol.

UMSCs-exo concentration detection

The concentration of UMSCs-exos was quantitatively determined using the bicinchoninic acid (BCA) method. BSA standards and proteins (25 μL each) were aliquoted into a 96-well plate, combined with 200 μL of BCA working solution per well, and incubated at 37°C for 30 minutes. Absorbance at 562 nm was measured using a microplate reader (BioTek, Winooski, VT, USA).

UMSCs-exo antigen identification

Western blotting was carried out to detect the expression of UMSCs-exo antigens. After lysis, proteins were treated with a sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) loading buffer, separated by electrophoresis, blotted onto a polyvinylidene fluoride (PVDF) membrane, and stained overnight at 4°C with primary antibodies. The primary antibodies were: Tsg101 (1:1000; Santa Cruz, Dallas, TX, USA), CD9 (1:1000; Abcam, Cambridge, UK), CD63 (1:1000; Abcam). Membranes were rinsed and counterstained with a peroxidase-conjugated anti-rabbit IgG horseradish peroxidase secondary antibody (1:2000; Abcam, Cambridge, UK). Enhanced chemiluminescent (ECL) reagent was used for visualization. Protein quantification was determined by densitometry.

Electron microscopic examination of UMSCs-exos

The freshly extracted exosomes underwent serial dilutions with Dulbecco's phosphate buffered saline (DPBS) and loaded onto a copper mesh. After 2 minutes of precipitation, the excess samples were absorbed by filter paper and dried for 5 minutes. Negative staining with 1% uranyl acetate was performed for 2 minutes, followed by a 40-minute drying period before electron microscopy (Tecnai G2 Spirit, USA). Furthermore, the size of the exosomes was measured by ZetaView PMX 110 (Particle Metrix, Meerbusch, Germany) using Nano Tracking Analysis (NTA).

Tumor cell source

Human breast carcinoma (BC, MDA-MB-231), gastric carcinoma (GC, BGC-823), lung carcinoma (LC, A549), and glioma cells (LN-229) were acquired from the American Type Culture Collection (ATCC).

Co-culture of UMSCs and tumor cells

UMSCs and tumor cells were co-cultured using microfluidic Transwell inserts, with UMSCs in the upper chamber and tumor cells in the lower chamber. For cell proliferation, migration, and invasion assays, 48-well plates (pore size: 0.4 μm), 6-well plates (pore size: 3 μm), and 24-well plates (pore size: 8 μm) were used, respectively.

Intervention treatment of UMSCs-exos

UMSCs-exos were added into the cell culture medium at a concentration of 200 μg/mL.

Cell proliferation assay

Cells were seeded into a 96-well plate (2000 cells/well). Cell counting kit-8 (CCK-8) solution (10 μL) was added into one well every 24 hours. Absorbance at 450 nm was measured using a microplate reader after 4 hours of incubation.

Scratch-wound assay

Dissociated cells adjusted to a density of 4×10^5/mL were seeded in six-well plates. Once reaching 80-90% confluence, a vertical scratch in the culture plate was made using a 10 μL pipette tip. Cell migration, calculated as (scratch distance$_{0\ h}$ - scratch distance$_{24\ h}$)/scratch distance$_{0\ h}$ × 100%, was observed after 24 hours.

Cell invasiveness assay

A Transwell assay was performed to assess cell invasiveness. Cells were starved in serum-free DMEM for 24 hours, then seeded into the upper chamber of a Transwell apparatus. DMEM supplemented with 15% FBS was added to the lower chamber. Following a 24-hour incubation period, cells were fixed with 95% ethanol and stained with 0.1% crystal violet for 20 minutes. Membrane-penetrating cells were then counted under a microscope.

Statistical analyses

Unless otherwise stated, all experiments were run independently with at least three replicates. Quantitative data are presented as

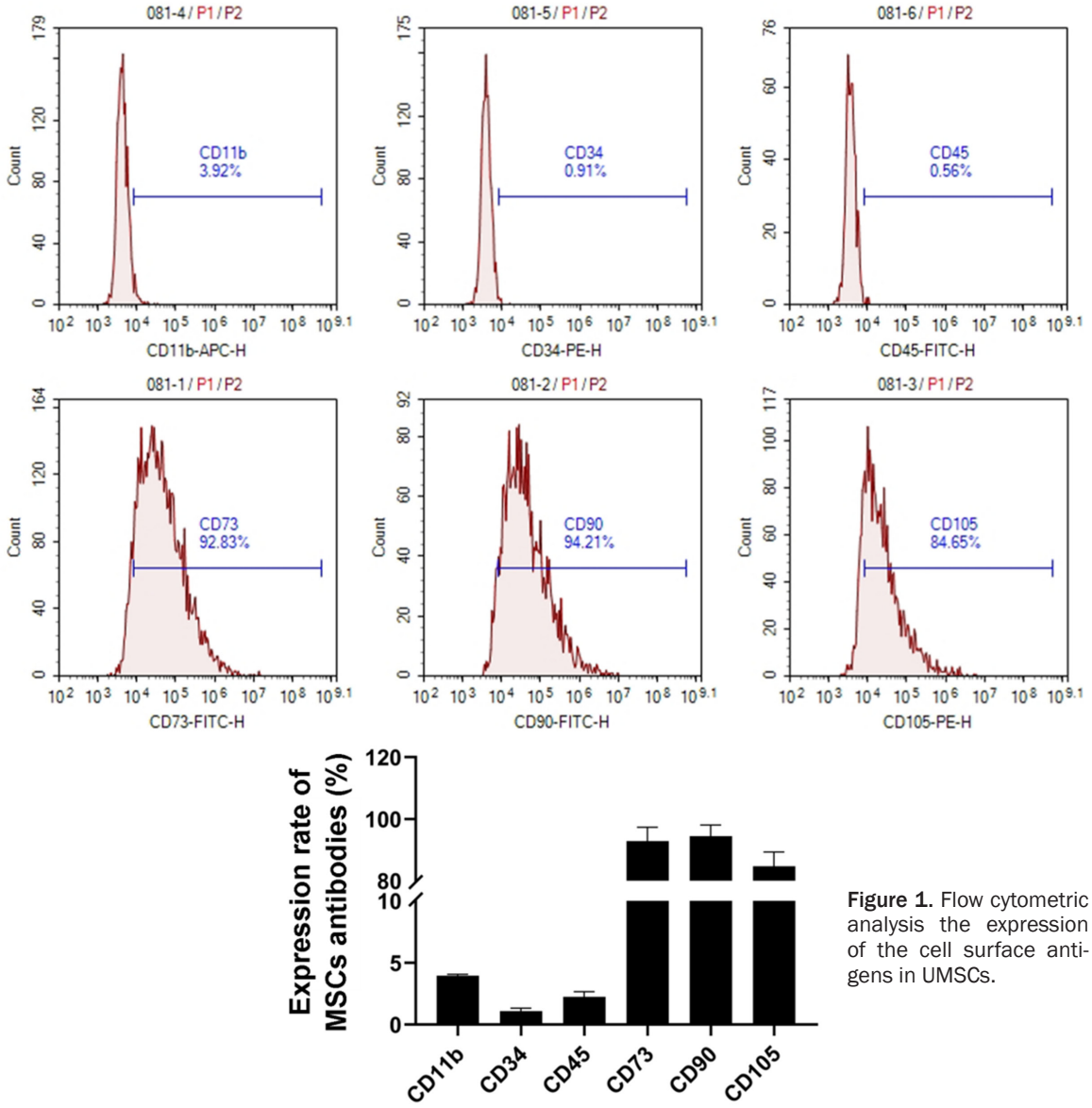

Figure 1. Flow cytometric analysis the expression of the cell surface antigens in UMSCs.

mean ± standard error. For comparisons between two groups, *p*-values were analyzed using the unpaired Student's t-test. Comparisons among more than two groups were made using one-way ANOVA followed by the Bonferroni test. A *p*-value <0.05 was considered statistically significant.

Results

UMSC isolation results

The results demonstrated that the expression levels of CD73, CD90, and CD105 in the isolated UMSCs were (92.90±4.46)%, (94.47±3.62)%, and (84.73±4.63)%, respectively. These findings indicate a high expression of positive surface antigens labeled by PE. Conversely, the levels of CD11b, CD34, and CD45 were (3.96±0.11)%, (1.09±0.24)%, and (2.24±0.42)%, respectively, signifying that the FITC-labeled negative surface antigens were expressed at low levels (**Figure 1**). These results confirm the successful isolation of UMSCs.

Differentiation potential of UMSCs

UMSCs were stained after being cultured in osteogenic, adipogenic and chondrogenic media. Alizarin red S staining revealed significant red calcium salt deposition in UMSCs. Similarly, oil red O staining displayed red, continuous oil

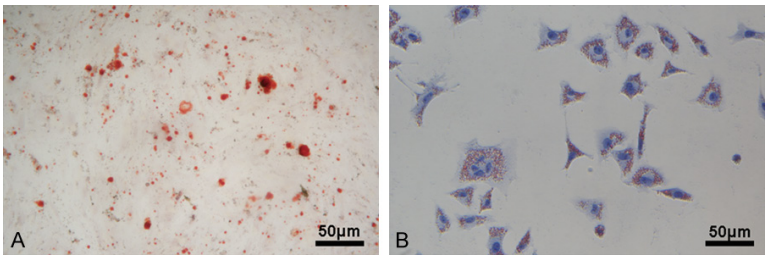

Figure 2. Differentiation potential of UMSCs. A. Alizarin red S staining. B. Oil red O staining.

droplets, indicating the osteogenic and adipogenic differentiation capabilities of UMSCs (**Figure 2**).

UMSCs-exo isolation results

Under electron microscopy, UMSCs-exos appeared as cup-shaped vesicles with diameters ranging approximately from 30-150 nm, exhibiting a clean background and a well-defined exo structure. The particle size measured about 126.62±1.64 nm, aligning with the typical size distribution of exos. Furthermore, exo marker protein detection revealed higher levels of Tsg101, CD9, and CD63 proteins in UMSCs-exos compared to UMSCs ($P<0.05$), confirming the successful separation of UMSCs-exos (**Figure 3**).

Influences of UMSCs and UMSCs-exos on cell proliferation

The CCK-8 assay indicated a significant enhancement in the proliferation capacities of A549, MDA-MB-231, and BGC-823 cells following both UMSC and UMSCs-exo interventions ($P<0.05$). Additionally, a comparison showed a reduced proliferation capacity in UMSCs-LN-229 and UMSCs-exo-LN-229 compared to LN-229, with the lowest proliferation capacity observed in UMSCs-exo-LN-229 ($P<0.05$) (**Figure 4**).

Influences of UMSCs and UMSCs-exos on cell migration capacity

Interventions with both UMSCs and UMSCs-exos resulted in altered cell migration abilities, as assessed by the scratch-wound assay. There was a significant increase in the migration of MDA-MB-231, BGC-823, and A549 cells, and a decrease in LN-229 cell migration following intervention ($P<0.05$). Furthermore, the effects of UMSC and UMSCs-exo interventions on BC, GC, LC, and glioma cell migration were more pronounced with UMSCs-exos ($P<0.05$) (**Figure 5**).

Impacts of UMSCs and UMSCs-exos on cell invasiveness

Both UMSC and UMSCs-exo interventions had minimal impact on the invasive ability of A549 cells ($P>0.05$). However, they significantly increased the invasion rates of BC and GC cells ($P<0.05$), whereas LN-229 showed decreased invasion following intervention ($P<0.05$). Notably, there were no significant differences in invasive capacity between cells treated with UMSCs and those treated with UMSCs-exos ($P>0.05$) (**Figure 6**).

Discussion

Neoplastic diseases rank as one of the most lethal disease types globally, posing significant threats to patient survival [14]. While patients with early-stage tumors may have favorable prognoses following comprehensive clinical treatment, advanced tumors often exhibit severe infiltration and lack effective clinical interventions [15]. MSCs and MSCs-exos play multifaceted roles in tumors, exhibiting anti-inflammatory effects to bolster immunity [16] and interacting with tumor cell-derived exos to modify tumor growth. This interaction allows for the potential therapeutic use of MSCs and MSCs-exos in states of tumor activity inhibition. Additionally, when a promoting effect is observed, key interaction factors can be identified for targeted inhibition, facilitating indirect therapy [17, 18]. In addition, MSCs-exos are also an excellent targeted drug carriers, potentially reducing drug side effects and extending drug half-lives, which is of considerable significance for most tumor chemotherapies [19]. Therefore, a thorough understanding of the effects of MSCs and MSCs-exos on tumors may offer crucial insights for future cancer treatment strategies.

This study presents a preliminary investigation into the effects of UMSCs and UMSCs-exos on tumor cell phenotypes. Due to the lack of uniform clinical guidelines for MSC isolation, it was necessary first to confirm the identity of isolat-

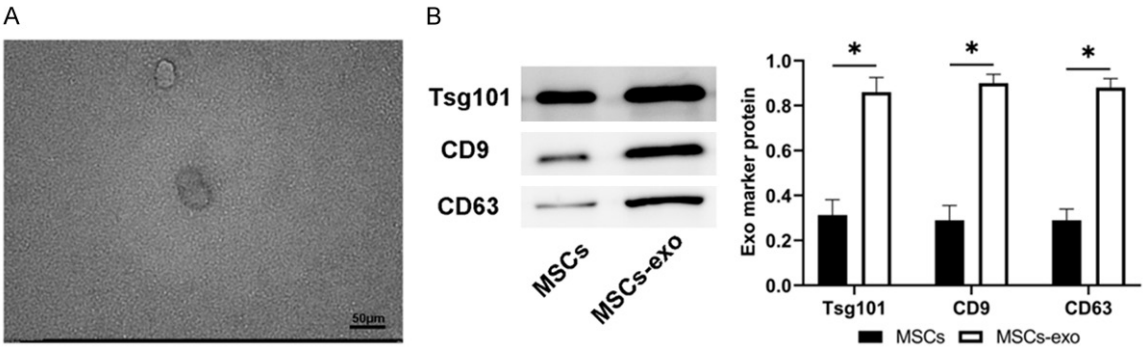

Figure 3. UMSCs-exo isolation results. A. Morphology of UMSCs-exos under transmission electron microscopy. B. Western blot analysis of the exo-specific CD9, CD63, and TSG101 proteins. *P<0.05.

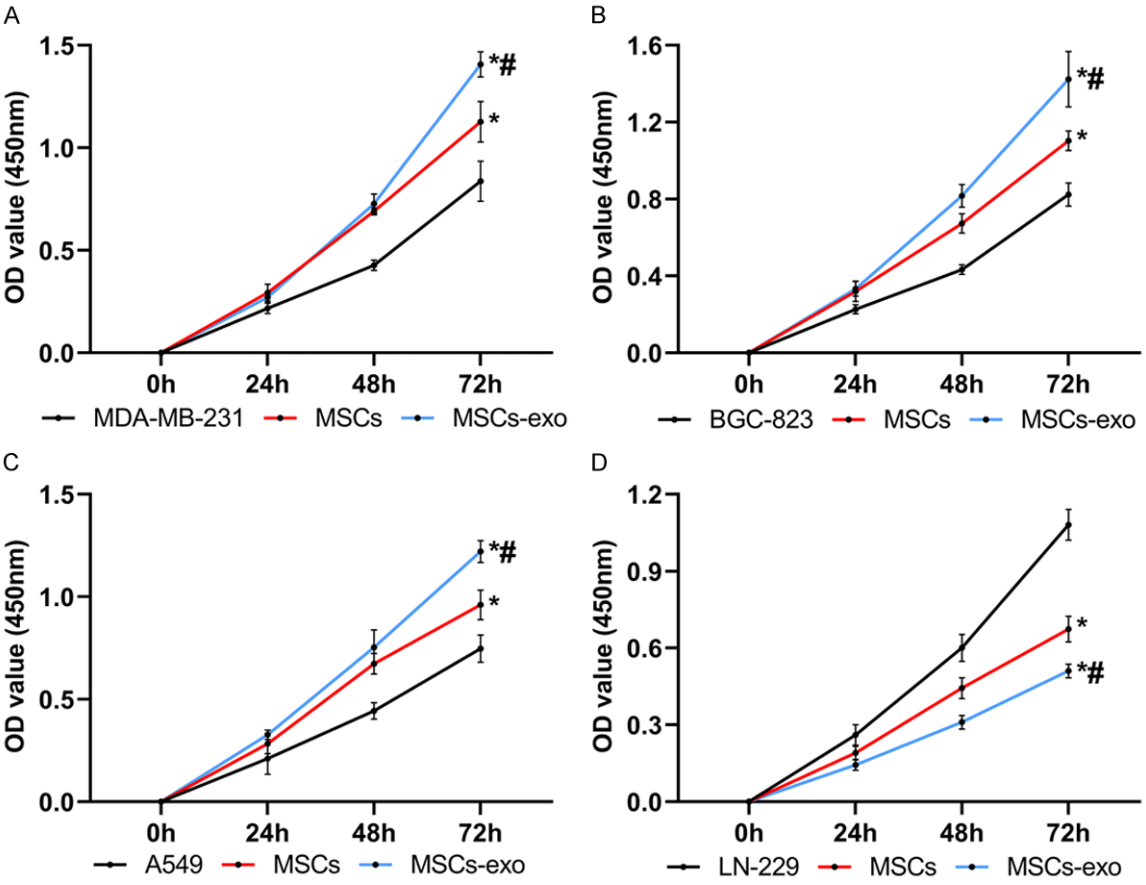

Figure 4. Influences of UMSCs and UMSCs-exos on cell proliferation. A. The growth curve of MDA-MB-231. B. The growth curve of BGC-823. C. The growth curve of A549. D. The growth curve of LN-229. Compared with normal tumor cells, *P<0.05; compared with tumor cells intervened by MSCs, #P<0.05.

ed UMSCs. The International Society for Stem Cell Research has established criteria for MSC characterization, including high expression of CD73/90/105 and low to negligible expression of CD11b/14/19/34/45/79a and HLA-DR, coupled with the potential for differentiation into at least two lineages (e.g., osteogenesis, adipogenesis, and chondrogenesis) [20]. In our experiments, PE-labeled positive surface antigens were highly expressed, while FITC-labeled negative surface antigens showed low expression levels; moreover, three differentiation assays confirmed the robust differentiation capability of UMSCs, thereby validating successful

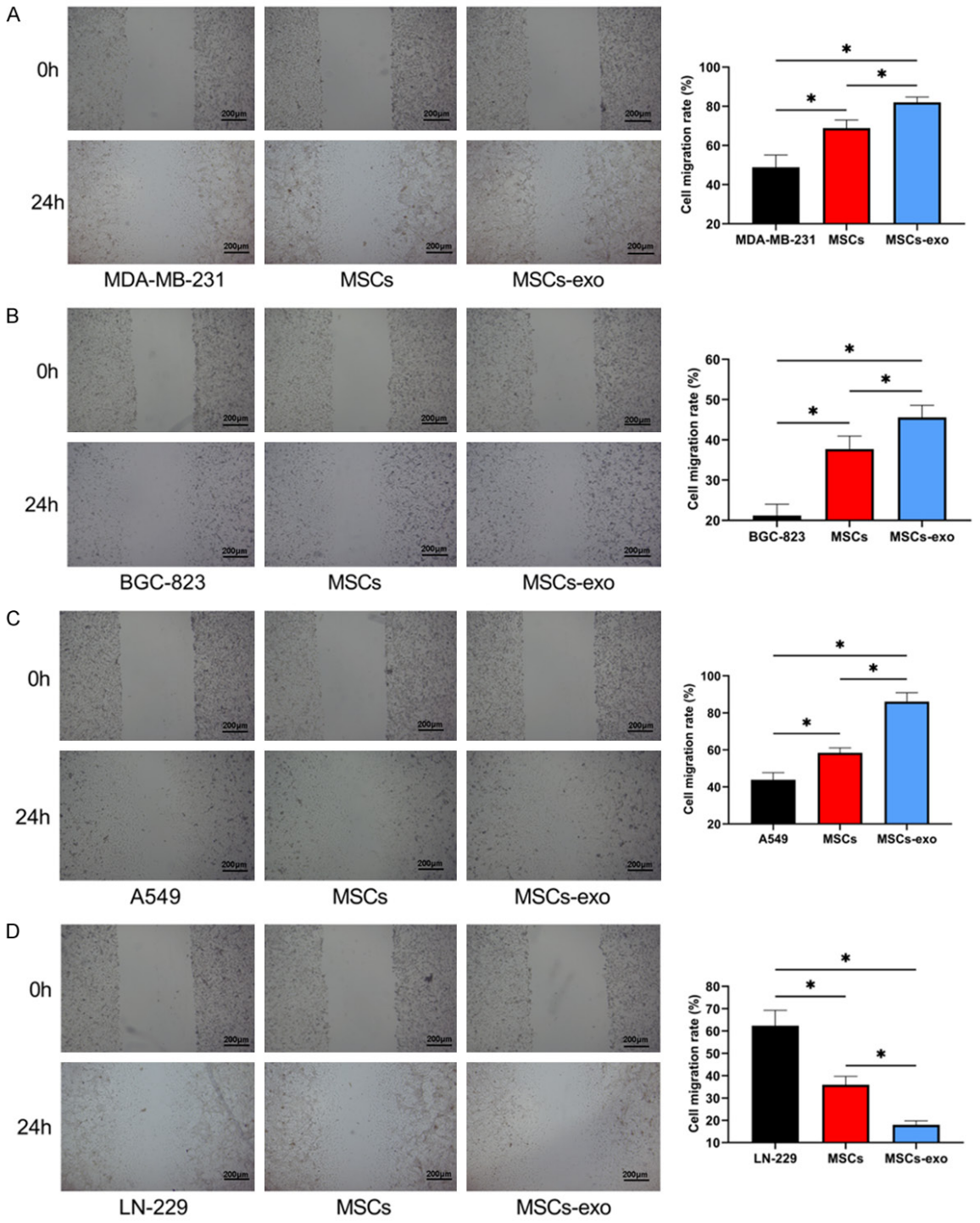

Figure 5. The effect of UMSCs and UMSCs-exos on tumor cell migration. A. The migration of MDA-MB-231. B. The migration of BGC-823. C. The migration of A549. D. The migration of LN-229. *P<0.05.

isolation. Li et al. also reported successful isolation of high-quality MSCs from rabbit umbilical cord [21]. Future comparative analyses could determine the most effective method for isolating UMSCs.

Exosomes are vesicles released by cells in vivo and in vitro for cellular communication, consisting of phospholipid membranes and proteins, and containing a large number of cell-derived molecules [22]. Differential centrifugation, the

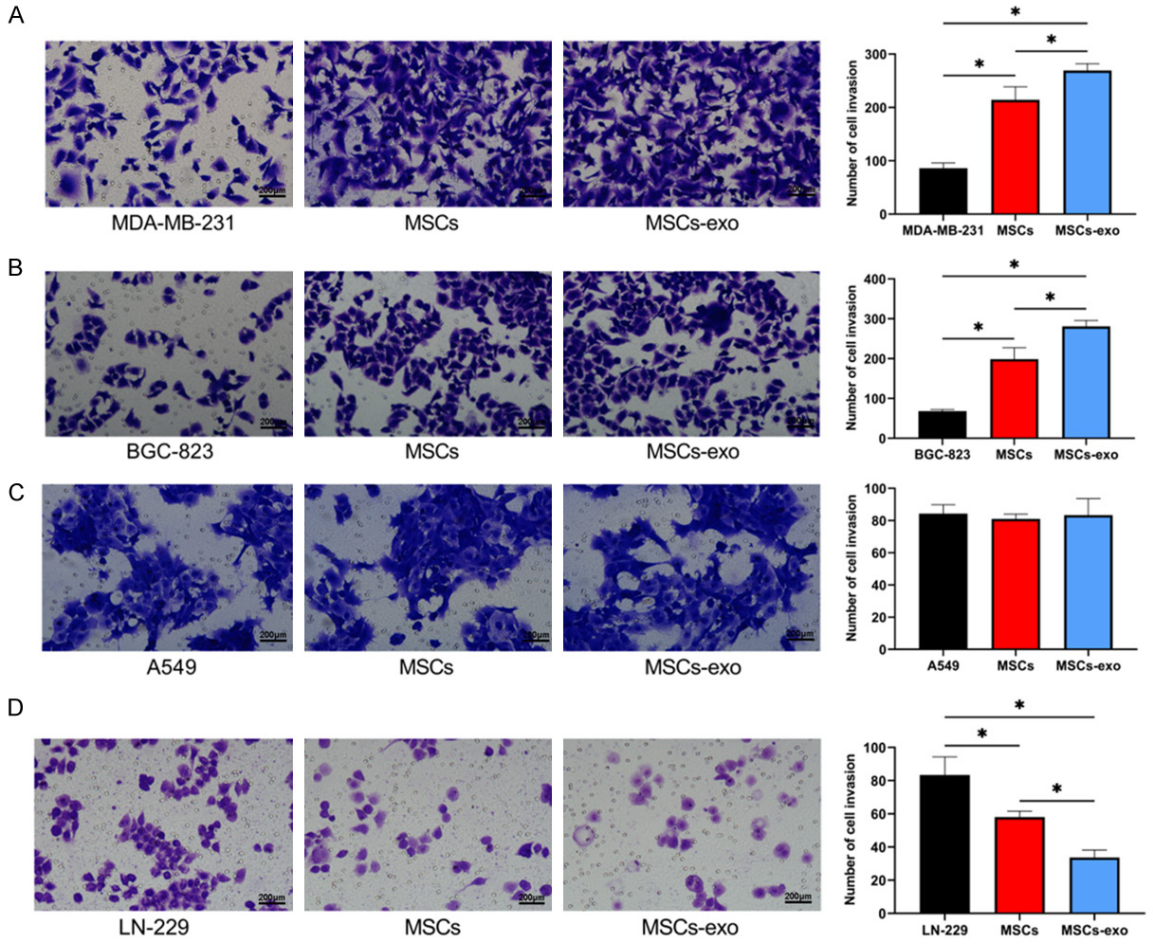

Figure 6. The effect of UMSCs and UMSCs-exos on tumor cell invasiveness. A. The invasion of MDA-MB-231. B. The invasion of BGC-823. C. The invasion of A549. D. The invasion of LN-229. *P<0.05.

main way to separate and extract exos from MSCs at present, has been indicated to cause the loss of a large number of nutrients in exos during the high-speed centrifugation process. Bovine serum culture medium can be used to address this deficiency [23]. Despite this, we employed a serum-free culture medium to ensure experimental accuracy, given the uncertainty of whether bovine serum culture medium affects tumor cells. Electron microscopy revealed that UMSCs-exos were cup-shaped, with particle sizes ranging from 110-150 nm, aligning with typical exosomal characteristics [24]. Additionally, enhanced expression of exosomal marker proteins Tsg101, CD9, and CD63 in UMSCs-exos confirmed their successful isolation.

This study focused on several common tumors to determine the influence of UMSCs and UMSCs-exos on their respective phenotypes. Breast cancer (BC), the most prevalent malignancy globally, has been shown to be influenced by lung MSCs, which can trigger lipid storage and activate the Hippo signaling pathway, thus promoting BC cell growth and metastasis [25, 26]. Our experimental results identified enhanced BC cell activity and increased migration and invasion capacities under UMSCs and UMSCs-exo co-culture, consistent with previous research, indicating that MDA-MB-231 may be regulated by both autologous tumor cell exos and UMSCs-exos. Corroborating previous research, UMSCs and UMSCs-exos also accelerated the growth phenotype of GC cells [27, 28].

Given that LC was the most common tumor worldwide before 2020, we also included LC cells in our analysis [29]. Our experimental

results demonstrated that A549 treated by UMSCs and UMSCs-exos exhibited phenotypes indicative of proliferation and migration. However, no significant changes were found in cellular invasion capacity, suggesting that the microenvironment created by UMSCs and the autophagy signals they induce could be potential targets for inhibiting the proliferation and migration of LC cells. In contrast to these findings, previous studies have shown that bone marrow MSCs can promote the invasiveness of A549 cells [30]. This discrepancy may be attributed to the different sources of MSCs. Therefore, we plan to conduct a validation analysis to further investigate these differences in the future.

Additionally, our research explored the effects of UMSCs and UMSCs-exos on glioma cells. We found that both UMSCs and UMSCs-exos effectively suppressed the activity, invasiveness, and metastasis of glioma cells, highlighting their potential as novel treatments for glioma. This is supported by previous studies which reported that MSCs and their exosomes can accelerate apoptosis and inhibit the growth of glioma cells [31, 32]. Together, these findings further underscore the clinical application value of UMSCs and UMSCs-exos.

In future studies, it will be crucial to confirm the influence of UMSCs and UMSCs-exos on actual tumorigenesis through in vivo tumor experiments. Additionally, identifying potential targets by analyzing gene expression profiles of tumor cells treated with UMSCs will help establish a more solid foundation for the clinical application of UMSCs.

Conclusion

UMSCs and UMSCs-exo can effectively promote the growth of BC and LC cells, while inhibiting the viability of GC and glioma cells. These findings hold significant implications for the future treatment of neoplastic diseases.

Disclosure of conflict of interest

None.

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