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Human Umbilical Cord Blood Derived (HUCB) Mesenchymal Stem Cells (MSc's) As an Alternative Therapeutics in Managing Infections

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ABSTRACT

Umbilical cord blood (UCB), considered medical waste, contains Mesenchymal stem cells (MSCs) in a mucous connective tissue known as Wharton's jelly. These cells exhibit the ability to self-renew and maintain multipotency while differentiating into various lineages. UCB provides a non-invasive and ethically uncomplicated source for MSC and UC-derived MSCs (UC-MSCs) are particularly valuable due to their immunomodulatory properties, making them promising candidates for regenerative medicine and immunotherapy.

This study aims to explore the current understanding of UC-MSCs, their differentiation potential, clinical applications, and the challenges faced in MSC therapy. The emergence of mesenchymal stem cells (MSCs) as a potential antimicrobial agent was also done. An attempt to optimize the culture conditions, cell sourcing, and standardization of protocols to maximize their therapeutic efficacy.

Keywords: *UCB, MSCs, stem cells, Umbilical cord.*

1. INTRODUCTION

Mesenchymal stem cells (MSCs) originate in the human embryo and are considered multipotent stem cells (Pittenger et al., 1999). MSCs are a heterogeneous subset of stromal stem cells, which can be isolated from the bone marrow, mobilized peripheral blood, cord blood, umbilical cord (UC), placenta, adipose tissue, dental pulp, and even the fetal liver and lungs (Dominici et al., 2006). UC contains two umbilical arteries (UCAs) and one umbilical vein (UCV), both embedded within a specific mucous connective tissue, known as Wharton's jelly (WJ), which is covered by amniotic epithelium (Troyer & Weiss, 2008). UC is considered medical waste, and the collection of UC-MSCs is non-invasive; furthermore, access to UC-MSCs has not been encumbered with ethical problems (El Omar et al., 2014). UC-MSCs, similarly to MSCs derived from other sources, have a distinct capacity for self-renewal while maintaining their multipotency, i.e., the ability to differentiate into adipocytes, osteocytes, chondrocytes, neurons, and hepatocytes, although some differentiation abilities are known to be partial (Kern et al., 2006). Moreover, UC-MSCs have also attracted great interest because of their immunomodulatory properties (Le Blanc & Mougiakakos, 2012). Nowadays, UC-MSCs are proposed as a possible versatile tool for regenerative medicine and immunotherapy (Wei et al., 2013).

Staphylococcus aureus is a Gram-positive spherically shaped bacterium, a member of the Bacillota, and is a usual member of the microbiota of the body, frequently found in the upper respiratory tract and on the skin (Tong et al., 2015). It is often positive for catalase and nitrate reduction and is a facultative anaerobe that can grow without the need for oxygen (Lowy, 1998). Although S. aureus usually acts as a commensal of the human microbiota, it can also become an opportunistic pathogen, being a common cause of skin infections including abscesses, respiratory infections such as sinusitis, and food poisoning (Otto, 2014). Pathogenic strains often promote infections by producing virulent factors such as potent protein

toxins and the expression of a cell-surface protein that binds and inactivates antibodies (Foster, 2005). S. aureus is one of the leading pathogens for deaths associated with antimicrobial resistance, and the emergence of antibiotic-resistant strains such as methicillin-resistant S. aureus (MRSA) is a worldwide problem in clinical medicine (Chambers & DeLeo, 2009). Despite much research and development, no vaccine for S. aureus has been approved (Fowler & Proctor, 2014).

MSCs will play an important role in managing many disorders (Caplan, 2007). MSCs have been shown to be beneficial in treating bone disorders, such as osteogenesis imperfecta (OI) and hypophosphatasia (Le Blanc et al., 2005). Despite improvements in medical and surgical therapies, heart disease and heart failure continue to show high morbidity and mortality rates (Menasché, 2008). MSC therapy is an attractive candidate for cardiovascular repair due to its regenerative and immunomodulatory properties (Liao et al., 2008). Based on their ability to modulate immune responses, MSCs have also been proposed as a treatment for autoimmune diseases (Uccelli et al., 2008). MSCs are emerging as vehicles for cancer gene therapy due to their inherent migratory abilities toward tumors (Djouad et al., 2003).

The umbilical cord contains two arteries and one vein, which are surrounded by mucoid connective tissue, and this is called Wharton's jelly (Mitchell et al., 2003). The cord is covered by an epithelium derived from the enveloping amnion (Troyer & Weiss, 2008). The network of glycoprotein microfibrils and collagen fibrils in Wharton's jelly has been previously studied (Sobolewski et al., 1997). The interlaced collagen fibres and small, woven bundles are arranged to form a continuous soft skeleton that encases the umbilical vessels (Parolini & Soncini, 2006). In Wharton's jelly, the most abundant glycosaminoglycan is hyaluronic acid, which forms a hydrated gel around the fibroblasts and collagen fibrils and maintains the tissue architecture of the umbilical cord by protecting it from pressure (Wang et al., 2004). The phenotypic stromal cells in Wharton's jelly are fibroblast-like cells (Karahuseyinoglu et al., 2007). However, cells with the ultrastructural characteristics of myofibroblasts have been found (Sarugaser et al., 2005). Recently, Mitchell et al. (2003) found that matrix cells from Wharton's jelly can be induced to form neurons and glia cells by treating with basic fibroblast growth factor and low-serum media plus butylated hydroxy anisole and dimethyl sulfoxide.

In this study, we demonstrate that mesenchymal cells from the umbilical cord blood, when expanded in culture, express adhesion molecules (CD44, CD105), integrin markers (CD29, CD51), and mesenchymal stem cell (MSC) markers (SH2, SH3) but not markers of hematopoietic differentiation (CD34, CD45) (Dominici et al., 2006). After exposure of these cells to cardiomyocyte-conditioned medium or 5-azacytidine, they expressed cardiac troponin-I and N-cadherin, indicating differentiation into cardiomyocytes (Hsieh et al., 2006). Under suitable culture conditions, these cells could also differentiate into osteogenic and adipogenic cells (Zuk et al., 2002). Thus, human umbilical cord mesenchymal cells can be expanded in culture and induced to form several different types of cells (Weiss et al., 2008). They may therefore prove to be a new source of cells for cell therapy, including targets such as stromal tissue and cardiac muscle (Liao et al., 2008). This will help to avoid several ethical and technical issues (El Omar et al., 2014).

2. MATERIAL AND METHODS

MATERIALS

The study was ethically approved and conducted under the Bangalore Medical College and Research Institute (No. BMCRI/EC/11/23-24)

Sample Collection: Mouse liver tissue and Human umbilical cord blood (HUCB)

HUCB from normal pregnancy and advanced maternal age pregnancy was collected from authorized maternity centres with prior consent of the subject strictly following the ethical norms and conditions.

First pregnancy of the individual between the age group of 18-42 will be considered (N=10).

HUCB was collected from both caesarean and normal delivery.

Inclusion criteria: Advanced maternal age pregnancy samples will be collected from the individuals during 3rd & 5th month of pregnancy.

Exclusion criteria: The subjects will be pre-evaluated in terms of gestational complications such as hereditary or drug induced diabetes, hypertension, thyroid and any other complications.

Fresh human umbilical cord blood was collected post-birth into EDTA and non-EDTA tubes, stored in Hanks' balanced salt solution for 12–24 hours before processing to isolate mesenchymal cells (Pittenger et al., 1999). The cord blood was centrifuged at 2500 RPM for 5 minutes at room temperature, washed with serum-free DMEM, then centrifuged again at 3000 RPM. Cells were treated with collagenase (2 mg/ml) for 16 hours at 37°C, washed, treated with 2.5% trypsin for 30 minutes at 37°C with agitation, and finally cultured in DMEM supplemented with 10% FBS and glucose (4.5 g/l) in a 5% CO2 incubator (Le Blanc & Pittenger, 2005).

Sample processing: Blood samples were collected using EDTA tubes and centrifuge tubes, and processed with trypsin,

Chemical reagents: DMEM, 5-azacytidine, and growth factor (TGF)-β1, alongside non-labelled mouse anti-human

antibodies, PBS, Oil Red O, and standard laboratory glassware (Dominici et al., 2006).

3. METHODOLOGY:

Cell Culture

The cord blood was centrifuged at 2500 RPM for 5 minutes at room temperature and the pellet was washed with serum-free Dulbecco's modified Eagle's medium (DMEM). Next, the cells were centrifuged at 3000 RPM for 5 minutes at room temperature and then treated with collagenase (2 mg/ml) for 16 hours at 37°C, washed, and treated with 2.5% trypsin for 30 minutes at 37°C with agitation. Finally, the cells were washed and cultured in DMEM supplemented with 10% fetal bovine serum (FBS) and glucose (4.5 g/l) in 5% CO2 in a 37°C incubator.

Induction of Cardiogenic Differentiation: For 5-azacytidine treatment, mesenchymal cells were incubated for 24 hours in serum-free DMEM containing 3 µM 5-azacytidine, followed by DMEM with 10% FBS for 3 days to 5 weeks to prevent cell death (Gnecchi et al., 2008). Cardiomyocyte-conditioned medium was prepared by culturing cardiomyocytes from 7-day-old rat hearts in DMEM with glucose and FBS for 72 hours. The medium was harvested, centrifuged at 8000 RPM for 10 minutes, and filtered for use (Trounson & McDonald, 2015).

Induction of Adipogenic, Chondrogenic, or Osteogenic Differentiation: Cells at passage 2 were incubated in differentiation media tailored for adipogenic, chondrogenic, and osteogenic lineages, with medium changes every 3 days. Differentiation was confirmed via histochemical staining and immunohistochemistry (Uccelli et al., 2008).

Characterization of Mesenchymal Cells in Umbilical Cord Blood: Cells were cultured in DMEM with glucose and FBS, exhibiting fibroblast-like morphology. Flow cytometry confirmed the expression of MSC markers (CD44, CD105, SH2, SH3) and absence of hematopoietic markers (CD34, CD45) (Gordon & Lowy, 2008).

Flow Cytometry: Extracted mesenchymal cells were cultured in DMEM with glucose and FBS for 5–7 days, trypsinized, and suspended at 5 × 10^6/ml. A 1-ml sample was incubated with non-labelled mouse anti-human antibodies for 45 minutes at 4°C, followed by FITC-conjugated anti-mouse IgG antibodies for 1 hour at room temperature (Horwitz et al., 1999). Cells were washed with PBS, centrifuged, and fixed in 4% paraformaldehyde. Control samples were incubated with PBS instead of the primary antibody (Mitchell et al., 2003).

Immunocytochemistry: Mesenchymal cells were cultured with differentiating factors for 3 days to 5 weeks. Fixed monolayers were blocked with goat serum, incubated with primary antibodies, then stained with FITC-conjugated secondary antibodies (Baksh et al., 2004). Slides were mounted and examined under a confocal microscope.

Western Blotting: Cells were lysed, and protein fractions were separated via SDS-PAGE, transferred to PVDF membranes, and probed with specific primary and HRP-conjugated secondary antibodies. Detection was performed using enhanced chemiluminescence (Chambers & DeLeo, 2009).

Histochemical Staining: Cells were fixed with paraformaldehyde and stained with Oil Red O, Toluidine Blue, or alkaline phosphatase, depending on the differentiation pathway. Immunohistochemical staining for type II collagen was performed for chondrogenic differentiation (Projan & Nesin, 2003).

Mechanical disaggregation

This technique basically involved carefully chopping or slicing of tissue into pieces and disruption by mild homogenization or by repeatedly forcing the tissue through a syringe with a wide base needle. 2.5g of liver tissue was taken in a petri dish containing 1-2ml of phosphate buffer saline. Fat and other tissues were removed, and the tissue was chopped into small bits using sterile surgical blade. The above chopped tissue was filtered using cheese cloth / muslin cloth. The chopped tissue was homogenized with 1:9 volume of phosphate buffer saline. The homogenized tissue was filtered using cheese cloth / muslin cloth. The filtrate obtained was centrifuged at 5000 RPM for 5 minutes and the obtained pellet was resuspended in 1ml of phosphate buffer saline. The cell suspension was taken into a hemocytometer and viability call percentage was calculated using trypan blue dye exclusion method. 20 microliter of cell suspension was mixed with 20 microliters of of trypan blue in a vial. The slide was focused under a microscope and the number of viable and non-viables cells in the four corners were counted and the percentage of viability was calculated. The cell dispersion was filtered through a 100 µm pore size cell strainer into a 50 ml Conical tube in order to remove connective tissues and undigested tissue fragments. The cells were suspended in 40ml DMEM media and centrifuged at 5000g for 3 min at 4 °C. The supernatant was aspirated, and cells were gently re-suspended Celin 40 ml cold DMEM to wash cells, the centrifugation was repeated. Supernatant was aspirated, and the cells were gently re-suspended cells with 25 ml DMEM and 25 ml 90% FBS solution in PBS was added into the tube and gently mixed. The tubes were centrifuged at 2000 RPM for 10 min at 4 °C and the dead cell were removed & Cell pellet was suspended in 30 ml warm DMEM, and then centrifugation was repeated. Count the cells within the cell suspension using a hemocytometer and determine cell viability by trypan blue staining.

Hepatocyte culture

In a typical prep with > 85% viable cells, the cell density should reach approximately 60-70% confluence, which allows for cell-cell contact while maintaining sufficient space for the hepatocytes to grow to their full cell size and yield a final confluence of 90-95%. In order to form an even monolayer of hepatocytes, in other words, to minimize the tendency for cells to aggregate in the central area of the t flask the plate was kept in the LAF for 30 minutes before placing them in incubator. The cells were cultured at 5 % CO2, after 4-h culture, the cells remained, serum free media was added to maintain morphology of the cells. The media was replaced every 2-day interval.

4. RESULTS:

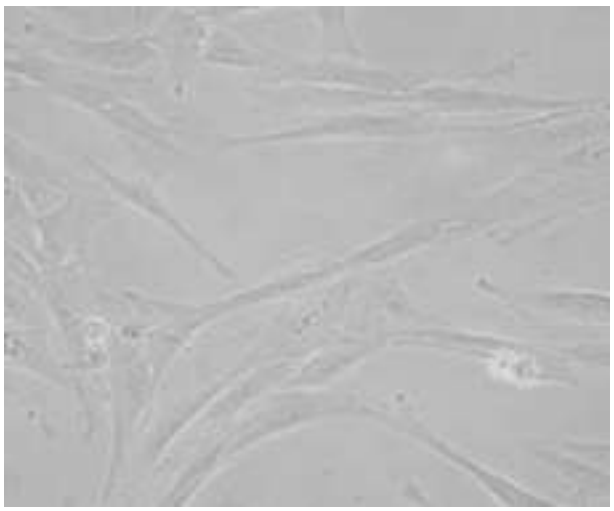

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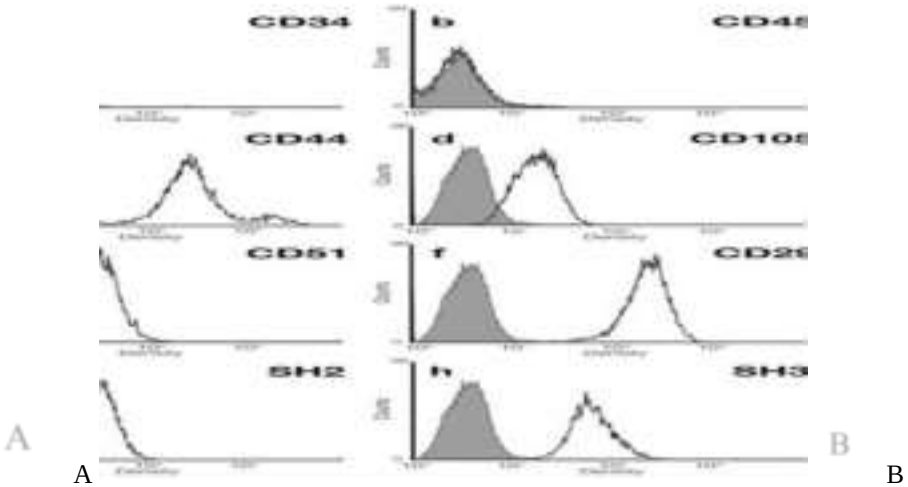
Fig 1A

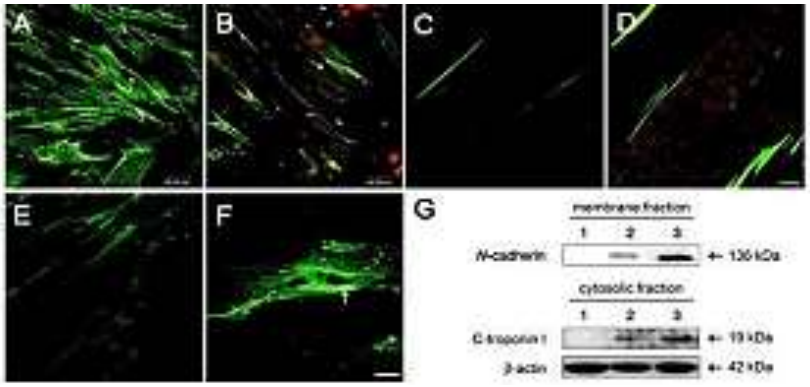


A B

(A) Cell cultures 3 days after the initial seeding of umbilical cord mesenchymal cells. The cells have a fibroblast-like morphology**.** (B): Flow cytometric analysis of surface-marker expression on umbilical cord mesenchymal cells. The cells were cultured in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum. After one passage at approximately 1 week, the cells were analyzed by flow cytometry. The shaded area shows the profile of the negative control. The data shown are representative of those obtained in six different experiments.

1.11 Cardiogenic Differentiation of Mesenchymal Cells in Umbilical cord blood

To investigate the potential of umbilical cord mesenchymal cells to differentiate into cardiomyocytes, 5-azacytidine (3 µmol/l), a drug that has been used to trigger this change, was added to the culture medium. We stained the cells with antibodies against human cardiac troponin I .



(A, C): Expression of cardiac troponin-I (red) and F-actin filaments (green) in untreated mesenchymal cells.

(B, D): Expression of cardiac troponin I and F-actin filaments in mesenchymal cells incubated with serum-free DMEM containing 3 µmol/l 5-azacytidine for 24 hours and DMEM/10% FBS for 21days.

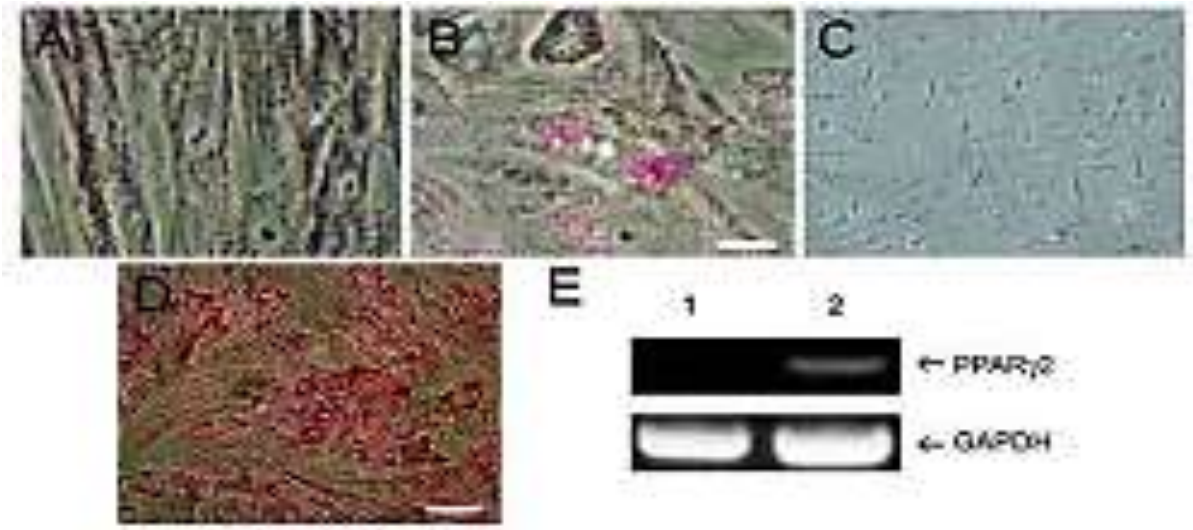
(E): Immunofluorescence staining of N-cadherin in untreated umbilical cord mesenchymal cells.

(F): N-cadherin expressed in the junctions between mesenchymal cells (arrow) cultured in cardiomyocyte-conditioned medium for 5 weeks. A and B, bar = 40 µm; C and D, bar = 10 µm; E and F, bar = 20 µm.

(G): Western blot showing N-cadherin and cardiac troponin I expression in, respectively, the membrane and cytosolic fraction of untreated and conditioned medium-treated umbilical cord mesenchymal cells

1.12 Adipogenic Differentiation of Mesenchymal Cells

Adipogenic differentiation, as seen by Oil red O–positive cells, was achieved by culturing the cells for 7 days in DMEM-l containing ascorbate, dexamethasone, and indomethacin.



Adipogenic differentiation of umbilical cord mesenchymal cells. **(A):** Control cells. **(B):** Cells in the adipogenic induction group showing varying degrees of staining for Oil red O at 7 days of culture (bar = 10 µm). **(C):** Control cells (bar = 25 µm). **(D):** Cells in the adipogenic induction group showing varying degrees of staining for Oil red O at 14 days of culture (bar = 25 µm). **(E):** RT-PCR analysis of untreated.

5. RESULT & INTREPRETATION:

Volume of small square = (area of small square) * (thickness of the coverslip)

= 0.0025*0.1

= 0.00025 mm3

Sl.no	Number of viable cells	Number of non-viable cells

1.	141	26
2.	126	23
3.	81	18
4.	55	8
Total	403	75
Average	100.7	18.75

Volume of the chamber = 1*1*0.1mm3=10-3 cm

Percentage viability: no. of viable cells/total cell count*100

403/478*100 =84.30%

6. DISCUSSION

In this report, we have focused on human cord blood derived MSCs and demonstrated their antibacterial effects on *S. aureus* in vitro. Specifically, MSC-conditioned medium with or without additional cells suppressed bacterial growth. On the other hand, bacteria incubated with MSCs in fresh control medium did not show any significant effect suggesting that MSCs secreted antibacterial factors in growth medium during the 24-h incubation period.

Also, our results showed that just 1-h incubation of bacteria with a conditioned medium is sufficient to suppress bacterial growth. In this study, ampicillin and streptomycin were used as positive antibacterial control.

It should be noted that we have purposely chosen to use an experimentally determined, low concentration of ampicillin that results in a mild, incomplete inhibition of bacteria growth, to allow room to measure the adjunct antibacterial activity of MSCs/ASCs.

In this manner, the “ampicillin and streptomycin equivalence” of the antimicrobial activity of ASCs/BM-MSCs may be estimated, providing a therapeutic measure for future clinical applications.

7. CONCLUSION

With their ability to differentiate into multiple lineages, secrete factors related to immune regulation, and migrate toward sites of inflammation, MSCs have many clinical implications. The results of multiple clinical trials using MSCs have been promising but also highlight the critical challenges that must be addressed in the future. More research is needed to determine the mechanisms and biological properties of MSCs to enhance their therapeutic efficacy in various diseases. Furthermore, the heterogeneity of the MSC population presents a challenge for generalized findings. Therefore, it is important to standardize the generation protocols, including cell culture conditions, source, passage, and cell density, as they may impact MSC phenotype as well as functions. Further randomized, controlled, multicenter clinical trials are necessary to determine the optimal conditions for MSC therapy. With further advances, MSCs will play an important role in managing many disorders that lack effective standard treatment.

Our findings clearly show that adult MSCs produce antibacterial bio factor that inhibit the growth of *S. aureus*. The potential application of MSCs as a biocompatible, adjunct treatment of musculoskeletal infections

Under suitable culture conditions, these cells could also differentiate into osteogenic and adipogenic cells. Thus, human umbilical cord mesenchymal cells can be expanded in culture and induced to form several different types of cells. They may therefore prove to be a new source of cells for cell therapy, including targets such as stromal tissue and cardiac muscle. This will help to avoid several ethical and technical issue MSCs will play an important role in managing many disorders. MSCs have been shown to be beneficial in treating bone disorders, osteogenesis imperfecta (OI) and hypophosphatasia. Despite improvements in medical and surgical therapies, heart disease and heart failure continue to show high morbidity and mortality rates. MSC therapy is an attractive candidate for cardiovascular repair due to its regenerative and immunomodulatory properties. Based on their ability to modulate immune responses, MSCs have also been proposed as a treatment for autoimmune diseases. MSCs are emerging as vehicles for cancer gene therapy due to their inherent migratory abilities toward tumors.

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