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*Original Article*

# Human umbilical cord mesenchymal stem cell transplantation restores hematopoiesis in acute radiation disease

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**Abstract:** Objective: Nuclear technology has been widely used in military and civilian fields, and radiotherapy is an effective and common form of treatment for cancer. However, acute radiation disease caused by high doses of radiation is a serious complication. The aim of this study was to investigate the chance of mitigating radiation-triggered hematopoiesis failure using human umbilical cord mesenchymal stem cell (HUCMSC) transplantation. Methods: Umbilical cords were obtained from three full-term female neonatus through cesarean section at Xinqiao Hospital. Bone marrow mesenchymal stem cells (BMSCs) were cultivated as depicted before. Briefly, monocytes were collected from bone marrow blood by means of density separation columns. An acute radiation disease mouse model was established to compare the restoration effect of HUCMSCs and BMSCs transplanted via the tail vein. The hematopoietic stem cell transplantation (HSCT) mouse model was obtained through bone marrow cell transplantation (BMCT) from C57BL/6 mice (H-2b, donor) to female CB6F1 mice (H-2b×d, recipient) after irradiation. The mice were divided into five groups, including control (saline), irradiated (radiation), bone marrow (HSCT, transplanted $1\times10^6$ BM cells), HUCMSC (transplanted a mixture of $1\times10^6$ HUCMSCs and $1\times10^6$ BM cells), and BMSC group (transplanted a mixture of $1\times10^6$ BMSCs and $1\times10^6$ BM cells). The blood condition results were used to test the radiation-induced inflammatory reaction, and bone marrow pathological staining (H&E) was used to determine the radiation-induced bone marrow hematopoiesis failure. Results: After radiation, HUCMSC transplantation significantly improved the survival rate. By analyzing the blood condition test, colony formation, and bone marrow pathology, it was found that the HUCMSC group demonstrated significant functional improvements in terms of the recovery from hematopoiesis failure and reduction of inflammatory reaction. Conclusions: HUCMSCs have more advantages over BMSCs in restoring and promoting the recovery of radiation-induced hematopoietic damage, thus having a new therapeutic potential for patients with acute radiation disease.

**Keywords:** Acute radiation disease, hematopoiesis failure, HUCMSC

## Introduction

Although the use of nuclear weapons is strongly prohibited throughout the world, the threat of nuclear war is always present. Besides, a high percentage of cancer patients receive radiation therapy (RT) to eliminate tumor burden. However, current RT techniques cannot target only to tumor tissues, and a large number of normal tissues are also irradiated [1]. The application of curative radiation doses is further limited by the high intrinsic sensitivity of normal tissues to ionizing radiation (IR) [2, 3]. In particular, a large dose (>1 Gy) within a short period of time can easily induce acute radiation disease, a systemic disease [4]. The radiation-induced bone marrow radiation disease is characterized by tissue injury and hematopoiesis failure, leading to severe anemia, bleeding, infections, and alterations in the hematopoietic population [5]. An urgent hematopoietic stem cell transplantation (HSCT) is the mere method to treat this disease [6]. However, its implementation is limited by low hematopoietic reconstitution, severe complications, and destroyed hematopoietic inductive microenviron-

ment (HIM). Therefore, the goals of the current research efforts were to develop schemes to keep the bone marrow microenvironment from the IR toxicity, thereby improving hematopoietic reconstruction.

Stem cell therapy is a potential option for preventing or treating common tissue impairments caused by radiation [7]. Mesenchymal stem cells (MSCs) have the ability to differentiate into cells of the mesodermal (bone, fat, cartilage cells) lineage and are extensively studied as a promising platform for cellular therapy to promote tissue repair [8]. Some studies have reported that MSCs could facilitate the engraftment of hematopoietic stem cells, promote reconstruction of the hematological and immune system subsequent to HSCT [9], and migrate into inflamed tissues and contribute to tissue repair. Our team has previously shown that the phenotypic and immunoregulatory properties of human umbilical cord mesenchymal stem cells (HUCMSCs) are similar to that of bone marrow mesenchymal stem cells (BMSCs) [10, 11]. Subsequently, we discovered that HUCMSCs not only promoted the reestablishment of hematopoietic lineages *in vivo*, but also accelerated megakaryocyte proliferation over BMSCs [12]. These findings have confirmed that HUCMSCs might have good potential to counteract radiation-induced bone marrow damage.

In this study, we first established an acute radiation disease mouse model and then identified the potential of HUCMSCs to improve adipogenic and osteoplastic differentiation. Next, MSCs were infused into an acute radiation disease mouse model, where the hematopoiesis recovery, colony formation, and bone marrow pathology were detected. These observations demonstrated that the HUCMSCs transplantation could repair HIM functional impairment and facilitate recovery after hematopoietic destruction.

## Materials and methods

### *HUCMSCs and BMSCs isolation and culture*

All participants signed informed consent, and this study was reported to and approved by the Ethics Committee of Xinqiao Hospital (Approval No. AMUWEC20171321). Umbilical cords were obtained from three full-term female neonates by cesarean section at Xinqiao Hospital, Chongqing, China. Umbilical cords were gently washed several times with PBS to eliminate blood from umbilical arteries and veins. Small umbilical cord Wharton's jelly fragments were added into T-25 flasks with DMEM/F12 (5 mL) containing 1% penicillin and streptomycin and 10% FBS.

BMSCs were separated and cultivated as described [13] before. Briefly, monocytes were collected from bone marrow blood through density separation columns (1.077 g/L, Pharmacia Biotech, Uppsala, Sweden). Cells were re-suspended in α-MEM (Gibco, USA) containing 1 ng/mL bFGF (Sigma, USA), 10% FBS (Hyclone, USA) and 1% penicillin and streptomycin.

Cells were cultivated at 37°C under 5% $CO_2$ atmosphere with saturated humidity. The medium was changed every 3 days, and cells that reached confluence were passed into fresh flasks from one dish to four dishes (Hyclone, USA).

### *Examination of surface markers*

The expressions of surface marker of HUCMSCs and BMSCs were detected (Miltenyi Biotec, Germany) after three passages. Cells were trypsinized, rinsed and re-suspended in PBS ($1\times10^6$ cells/mL). Cell suspension (0.1 mL) was transferred into tubes (1.5 mL). Tube 1 was taken as the negative control (buffer), and the experiment tubes were cultivated with CD73-APC (clone TY/11.8; BioLegend, San Diego, CA, USA dilution ratio: 1:100), CD90-FITC (BD Biosciences, Lexington, KY; Cat# 5555951, dilution ratio: 1:100), CD105-PE (Biolegend, Cat# 800503 dilution ratio: 1:100), MSC Phenotyping Cocktail and Isotype Control Cocktail for 0.5 h. Flow cytometry was subsequently applied to analyze these cells.

### *Osteogenesis and adipogenesis differentiation*

HUCMSCs and BMSCs were cultured in corresponding media for 21-28 days. The media were replaced every 2-3 days. Osteogenic phenotype was confirmed through Alizarin Red S (ARS) staining. Cells were fixed with 4% HCHO for 0.5 h, rinsed with PBS, and subjected to ARS (pH 4.2) staining for 10 min. The microscope (Nikon, Japan) was used to take photomicrographs. The cells were in parallel exposed

to Oil Red O to confirm adipogenesis differentiation.

*Mouse model of acute radiation disease*

Female first generation CB6F1 mice (H-2b×d), a cross of C57BL/6F (H-2b) and BALB/c (H-2d) mice (10-12 weeks, 20-25 g), were bought from the Laboratory Animal Center of Third Military Medical University. Animals were confined in specific pathogen-free (SFP) rooms of the Second Affiliated Hospital.

$^{60}$Co-radiation (8.0 Gy, dose rate 30 Gy/10 min) was used to simulate severe damage of hematopoiesis function to establish acute radiation disease models [14]. The Ethics Committee of Xinqiao Hospital approved the animal experiments (Approval No. AMUWEC20171321).

*Transplantation in the acute radiation disease model*

The HSCT mouse model was obtained through BM cell transplantation (BMCT) from male C57BL/6 mice (H-2b, donor) to female CB6F1 mice (H-2b×d, recipient) after irradiation. The recipient female CB6F1 mice were administrated with $1\times10^6$ BM cells of donor with or without $1\times10^6$ MSCs. To explore the role of MSCs in acute radiation disease, MSCs were administered (i.v.) during BMCT. After radiation with 8.0 Gy $^{60}$Co for 8 h, cells or normal saline was injected into each group of mice through tail vein. There were a total of five groups and each group contained 25 mice: control group (CK); irradiated group; HSCT group (transplanted $1\times10^6$ BM cells); HUCMSC group (transplanted a mixture of $1\times10^6$ HUCMSCs and $1\times10^6$ BM cells); BMSC group (transplanted a mixture of $1\times10^6$ BMSCs and $1\times10^6$ BM cells). These mice were confined in SFP animal rooms.

*Chimerism rate determination*

FISH (Fluorescence in Situ Hybridization) was used to test the implantation status in mice. At day 28, one mouse from each group was sacrificed through neck dislocation. The bilateral femur and tibia were immersed in 75% alcohol for 300 s, separated with bone forceps and optical tweezer and placed in PBS. Bone marrow was rinsed with a 7-gauge-needle syringe (1 mL), and 7-, 5-, and 4-gauge needles were successively utilized for filtering cells to single-cell suspensions. Several drops of cell suspensions were put on the glass slides and then placed on a heating plate to dry. Ten microliters of Mouse Chromosome Y Painting Probe (orange) and Mouse Chromosome X Painting Probe (green) were mixed and added to the cell suspensions. Slides were placed in the fluorescence in situ hybridization instrument at 37°C. After 16 h, 10 μL DAPI dye was added. Fluorescence microscope was used to observe cell chromosome hybridization.

*Colony formation assay [15]*

One mouse from each group at day 7 and 28 was sacrificed through neck dislocation. After trypsinization of cells in logarithmic growth phase, complete medium (basal medium +10% fetal bovine serum) was resuspended into cell suspension and counted. Cell inoculation: 400-1,000 cells/well was inoculated in each experimental group in a 6-well culture plate (determined according to cell growth, generally 700 cells/well), followed by continuous cultivation for 14 days or until the number of cells in most single clones was greater than 50. The medium was changed every 3 days in the middle and the cell status was observed. After cloning was completed, pictures of the cells were taken under a microscope, and then cells were washed with PBS once, followed by adding 1 mL of 4% paraformaldehyde to each well for fixation for 30-60 min, and washed once with PBS. 1 mL crystal violet staining solution was added to each well, and the cells were stained for 10-20 min. The cells were washed with PBS several times and dried, and photos were taken with a digital camera (photograph the entire six-well plate and each well separately). Monocytes from bilateral femur were cultivated *in vitro* for CFU-E, BFU-E, CFU-GM, and CFU-GMEM. Each flask included $2\times10^5$ monocytes.

*Observation of pathological sections of bone marrow following transplantation*

One mouse from each group at days 7 and 28 was sacrificed through neck dislocation, and bilateral tibia was taken out to make bone marrow pathological sections. After fixed in 40% neutral HCHO, the specimens were embedded with paraffin. The resulting specimens were sectioned at a thickness of 5 μm and presented with H&E staining.

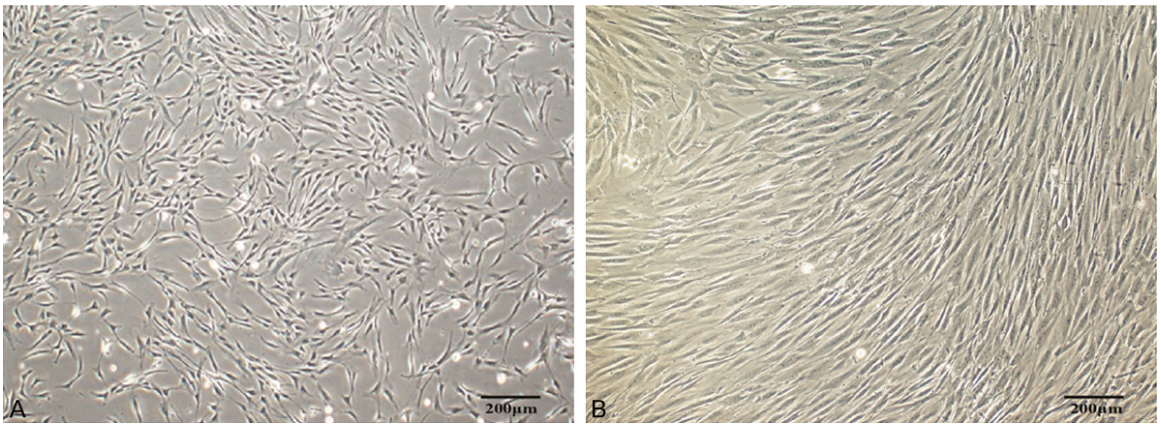


**Figure 1.** Morphological appearance of HUCMSCs and BMSCs. A. HUCMSCs after the second passage, on the third day of culture, reached 90% confluence (100×). B. BMSCs after the second passage, on the third day of culture, reached 90% confluence (100×).

*Data analysis*

Data were expressed as mean value ± SD. *t*-test was applied to analyze data significance. One-way analysis of variance was used for measurement data among multiple groups. $P<0.05$ meant significant difference. Data were analyzed through Prism 7.0 (GraphPad, La Jolla, CA, USA).

## Results

*HUCMSCs' extraction, proliferation, measurement and differentiation*

HUCMSCs and BMSCs were successfully extracted through tissue block attachment method and density gradient centrifugation. These MSCs reached -80% confluency 21 days later and were subsequently trypsinized and passaged ($1\times10^5$ cells/mL). HUCMSCs (**Figure 1A**) and BMSCs (**Figure 1B**) proliferated very rapidly and achieved confluency every 3 days following the first passage. Following the third passage, the cells were used to detect surface markers. Both HUCMSCs (**Figure 2A**) and BMSCs (**Figure 2B**) exhibited strong positivity for CD73, 90 and 105, whereas negative for CD14, 20, 34 and CD45, which were consistent with the literature [16]. The $4^{th}$ passage HUCMSCs and BMSCs were presented with an osteogenesis medium for 21-28 days to determine the differentiation. The resultant cultures exhibited osteoid generation and brown calcium deposition, as displayed by ARS. HUCMSCs and BMSCs adipogenesis differentiation was observed at day 21-28. Adipocytic phenotypes were characterized by the presence of tiny cell cytoplasm lipid droplets in cells; these lipid granules were subjected to Oil Red O staining (**Figure 3**). The above-mentioned characteristics were in line with the minimum standard for the identification of multipotent mesenchymal stem cells [17, 18].

*HUCMSC transplantation increases survival rate of mice with acute radiation disease*

In the present study, CB6F1 (H-2b×d) mice were first used as recipients to be exposed to $^{60}$Co-radiation (8.0 Gy). HUCMSCs and BMSCs were introduced (IOCV) into nude mice. The mice were classified to five groups. The CK did not receive radiation, but was only injected with normal saline, and the injection time was the same as that of other groups. Irradiated group was injected with normal saline after radiation, HSCT group with $1\times10^6$ BM cells, HUCMSC group with $1\times10^6$ HUCMSCs and $1\times10^6$ BM cells, and BMSC group with $1\times10^6$ HUCMSCs and $1\times10^6$ BM cells. None of the mice in control group died after injecting saline, while all mice in irradiated group died within 14 days. Further, HUCMSC and BMSC groups, which received MSCs, showed better survival rates compared to the HSCT group, which received only BM cells ($P<0.01$). Besides, a significant increase in the survival rate of HUCMSC group was observed as compared with that of BMSC group ($P<0.001$) (**Figure 4**).

*Chimerism rate detection*

The purpose of chimerism rate test was to detect whether the HSCT was successful in the experiment and whether it was completely

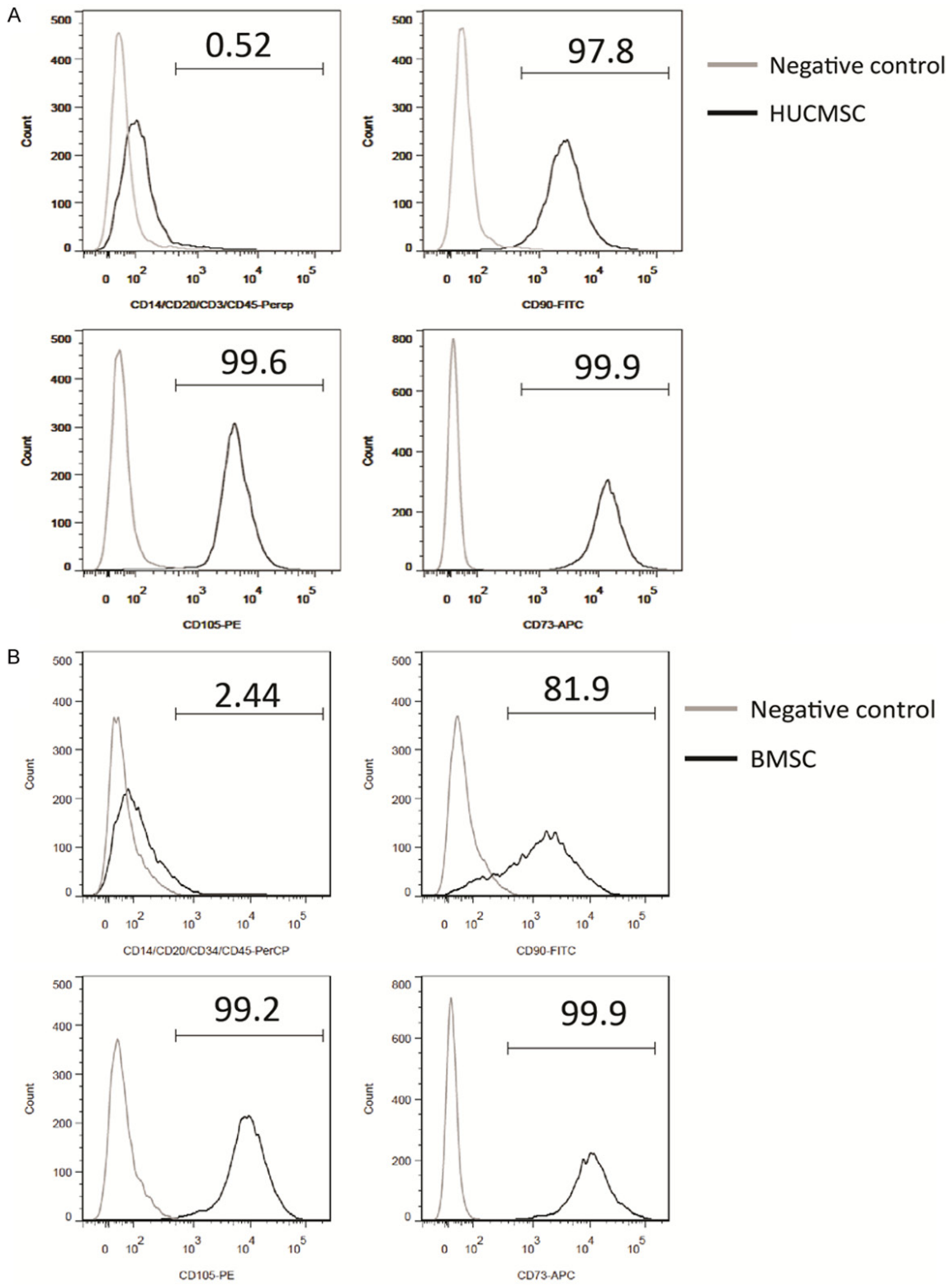


**Figure 2.** Identification of HUCMSCs and BMSCs. Third-passage HUCMSCs and BMSCs were collected and stained with CD14-PerCP, CD20-PerCP, CD34-PerCP, CD45-PerCP, CD73-APC, CD90-FITC, and CD105-PE. And then, HUCMSCs and BMSCs were detected by flow cytometry. A. HUCMSCs; B. BMSCs.

transplanted. FISH was used to test the implant status in mice 28 days after the transplantation of CB6F1 (H-2b×d). The red and green represented X and Y signals, respectively. The

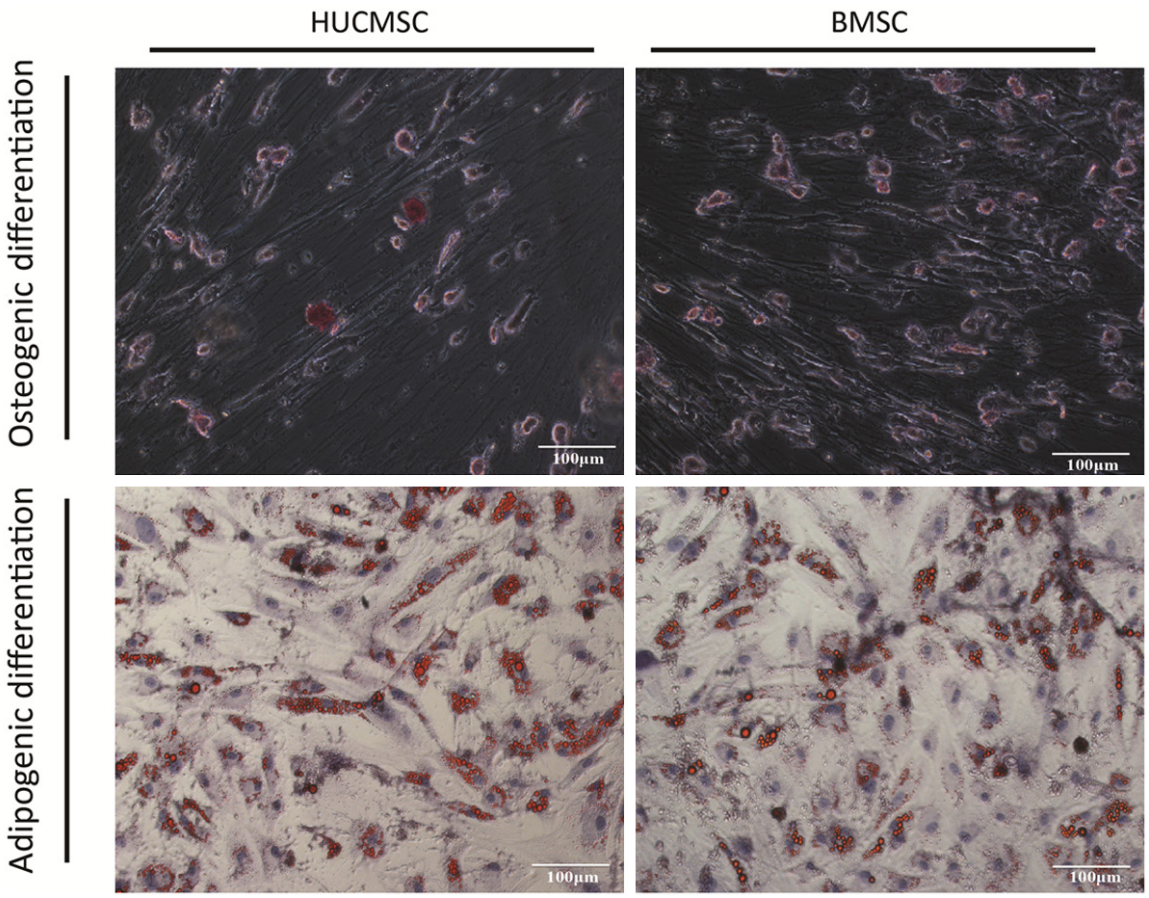


**Figure 3.** Osteogenic differentiation and adipogenic differentiation of HUCMSCs. Fourth-passage HUCMSCs and BMSCs were exposed to osteogenic or adipogenic medium for 3-4 weeks. Osteogenic differentiation was characterized by brown calcium deposition and osteoid formation as shown by Alizarin Red S. Adipogenic differentiation was signaled by the appearance of tiny intracytoplasmic lipid droplets in cells; these lipid granules were stained with Oil Red O (200×).

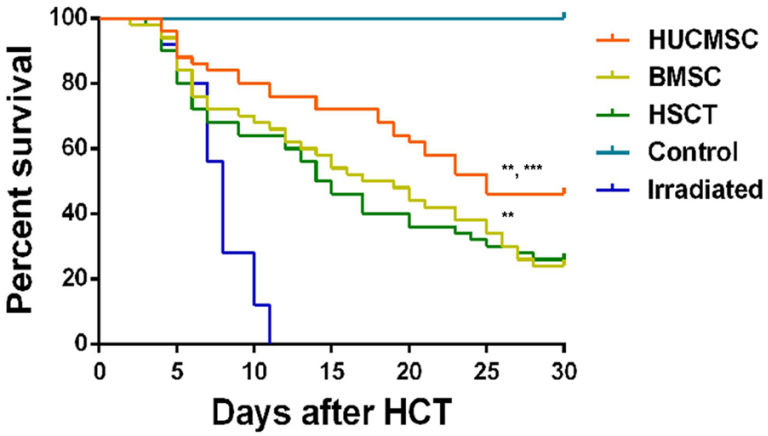


**Figure 4.** Survival rates in mice after transplantation. Kaplan-Meier survival curve for saline injected mice (control group), mice subjected to radiation alone (irradiated group), mice after BMCs administration (HSCT group), mice after administration of BMCs and HUCMSCs following radiation (HUCMSC group) and those supplemented with BMSCs (BMSC group). Compared with HSCT group, $^{**}P<0.01$; compared with BMSC group, $^{***}P<0.001$.

results showed that hybridization signals were detected in the bone marrow of each group. The chimerism rates were 96%, 97.2%, and 98.5%, respectively (**Figure 5**).

*HUCMSCs transplantation improves hematopoietic reconstruction in mice with acute radiation disease*

The results of routine blood test showed that WBC counts in the irradiated group were decreased significantly on day 1 and thereafter fluctuated at a lower level (**Figure 6A**). PLT counts were decreased rapidly on day 3 and kept reducing

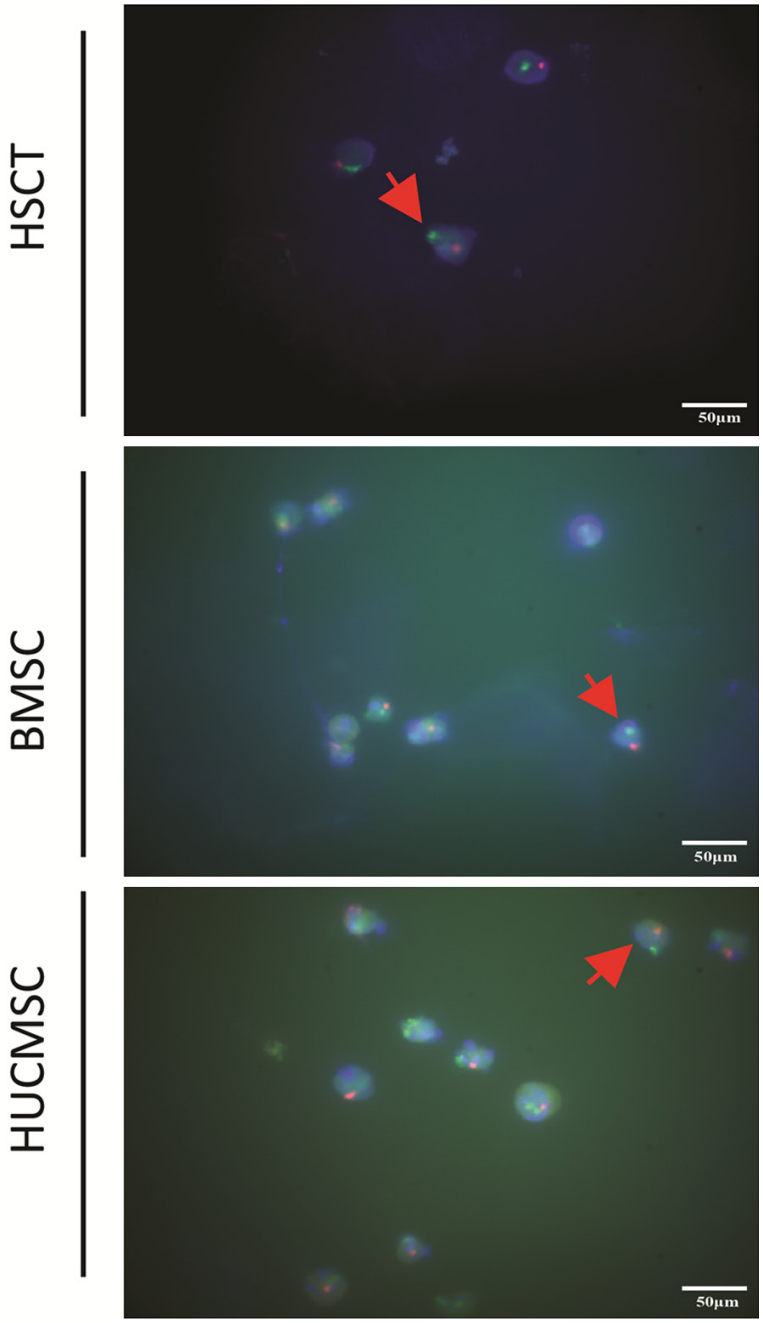


**Figure 5.** Chimerism rate detection. FISH was used to observe fusion signals in mice after transplantation (red arrows). The red and green represented Chromosome X and Chromosome Y signals, respectively.

till death (**Figure 6D**). RBC counts and HGB concentrations were declined significantly on day 7 and kept reducing till death (**Figure 6B**, **6C**).

The peripheral WBC counts in CB6F1 mice from each group started to decrease on day 1 after transplantation, exhibited the lowest level on day 5, and subsequently rose progressively. On day 10, HUCMSC group exhibited dramatically higher WBC level than that of BMSC and HSCT groups. On day 28, the WBC levels of HUCMSC and BMSC groups went back to the same level as that of control group, while those didn't happen in HSCT group (**Figure 7A**).

The PLT counts in all groups quickly reduced at day 1 after transplantation. The PLT counts of HUCMSC group, BMSC group and HSCT group exhibited the lowest level at day 7 and subsequently rose progressively. At day 14, the PLT counts in HUCMSC group were higher than those in other groups (**Figure 7D**).

The peripheral RBC and HGB counts in CB6F1 mice of the three groups had no significant difference (**Figure 7B**, **7C**).

*HUCMSCs transplantation ameliorates radiation-induced bone marrow hematopoiesis failure*

Bone marrow pathological staining (H&E) showed that in the irradiated group, degree of hyperplasia was reduced, the bone trabeculae was destroyed, and the number of scattered hematopoietic progenitor cells was decreased (**Figure 8A**). On day 7, the degree of hyperplasia was increased in HUCMSC and BMSC groups, whereas that in the HSCT group exhibited the lowest level (**Figure 8B-D**). On day 28, the degree of hyperplasia was increased in all groups and the number of nucleated cells was raised, with the highest numbers in the HUCMSC group and the lowest in the HSCT group (**Figure 8E-G**).

*HUCMSC transplantation facilitates colony formation*

On day 7, CFU-E, BFU-E, CFU-GM, and CFU-GEMM colony numbers were reduced, which were significantly lower in the HSCT group than

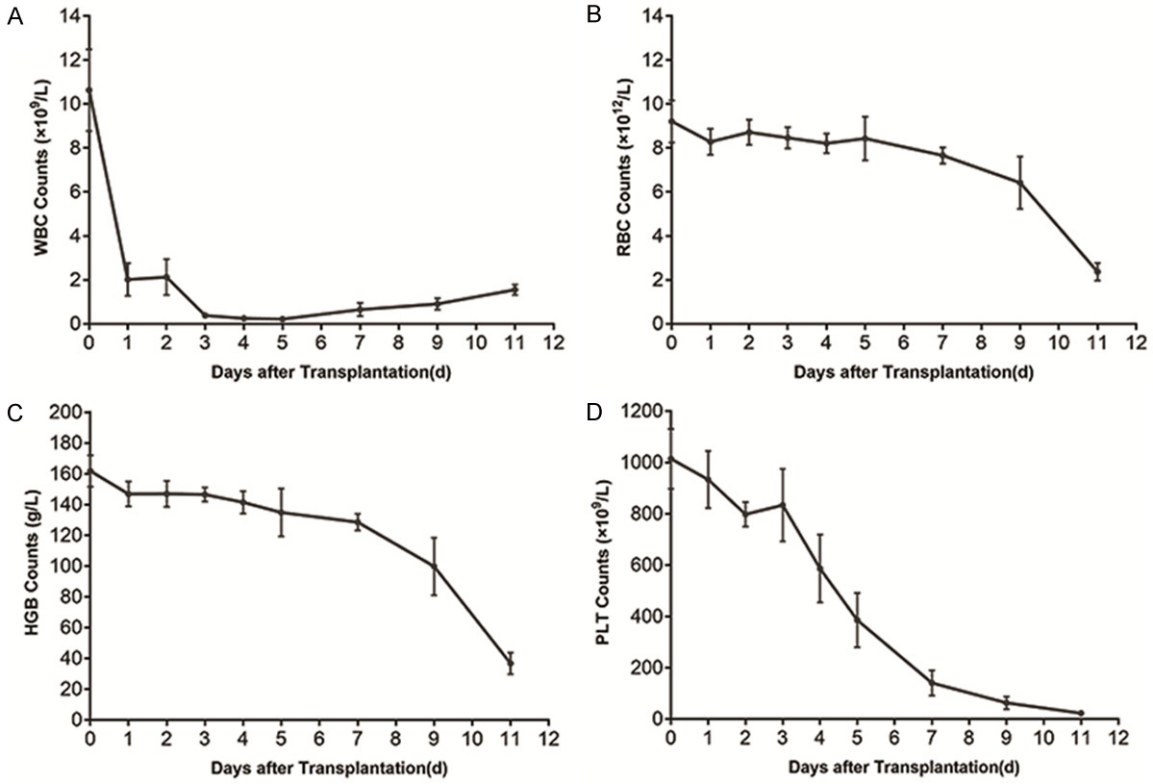


**Figure 6.** Blood routine results of mice after radiation (Irradiated group). A. WBC count; B. RBC count; C. HGB count; D. PLT count.

those in the co-transplantation group ($P<0.05$) (**Figure 9A**). On day 28, colony number in each group was increased, which corresponded with blood routine (**Figure 9B**). CFU-E, BFU-E, CFU-GM, and CFU-GEMM colony numbers in HUCMSC group were dramatically higher than those in the other two groups ($P<0.05$) (**Table 1**).

## Discussion

In severe acute bone marrow radiation disease, degree of marrow hyperplasia is significantly reduced, the structure of hematopoietic cells is destroyed, and the HIM is severely damaged. HSCT is the main treatment method, but it becomes inefficient because of the destruction of HIM [19]. Therefore, HIM needs to be restored simultaneously during the HSCT.

Due to the hematopoietic and immunomodulatory properties of MSCs, co-infusion of MSCs and HSCs can promote hematopoiesis and reduce the complications of transplantation in severe acute bone marrow radiation disease [20, 21]. However, MSCs from different sources are not entirely the same, and it is not clear whether the effects on HIM reconstruction are similar. A recent study showed that BMSCs could help promote hematopoietic reconstruction [22]. Our previous research indicated that the application of HUCMSCs in clinical treatment was satisfactory [23]. However, there is no relevant report on the effect of MSCs in hematopoietic reconstruction. Therefore, our research mainly focused on determining the effects of HUCMSCs in restoring the HIM of severe bone marrow acute radiation disease, and whether the treatment of HUCMSCs is superior to BMSCs.

HUCMSCs were isolated and obtained from the Wharton's Jelly without enzymatic treatment by cutting the cord in segments of -1 cm in length, which were further minced into submillimeter-sized particles and placed directly in the medium. HUCMSCs were proved to have the same surface antigens and abilities of osteogenesis and adipogenesis with BMSCs, providing a novel hematopoiesis resource. In our current study, C57BL/6 (H2-b) was selected as the donor, C57BL/6 (H2-b) and BALB/c (H2-d) hybrid gen-

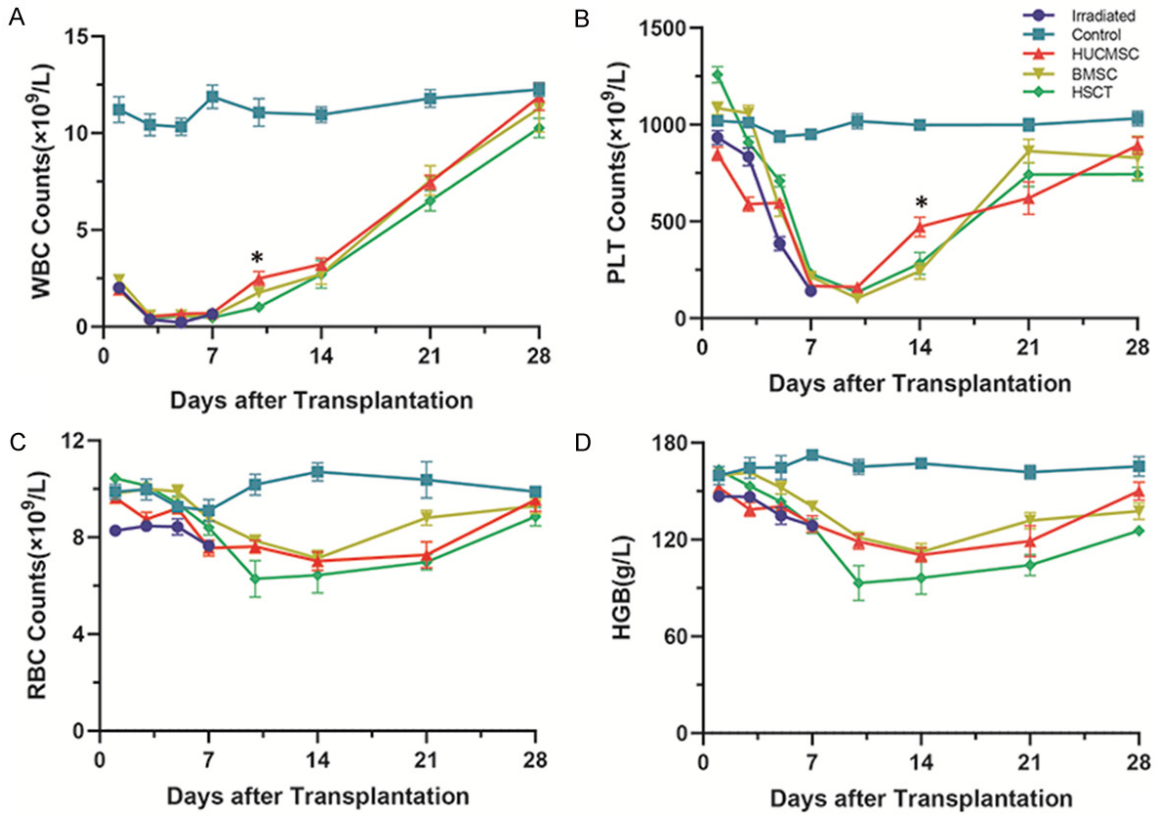


**Figure 7.** Blood routine results of mice of different group after transplantation. A. WBC count; B. RBC count; C. HGB count; D. PLT count. *$P$<0.05.

eration (CB6F1 (H2-b(d)) were selected as the host, and 8.0 Gy dose radiation was used to construct severe bone marrow radiation disease mouse model. The irradiated F1 mice were divided into blank control, HSCT, HUCMSC, and BMSC groups to observe whether the hematopoietic reconstruction of F1 mice was different. Our results showed that the blood routine of irradiated mice dropped after radiation, and all mice died before day 15 after radiation because of hematopoiesis failure, which suggested that our acute bone marrow radiation disease mouse model was feasible. Co-transplantation with HUCMSCs prolonged the survival rates of F1 mice, and the HUCMSC group showed faster and better hematopoietic recovery than other groups. Besides, after transplantation, the proliferation of bone marrow nucleated cells, and colony formation were significantly higher in the HUCMSC group.

The use of umbilical cord does not cause invasive damage to maternal body, thus addressing the ethical issues associated with the use of embryonic stem cells. HUCMSCs exhibit more primitive characteristics than adult stem cells, expressing some embryonal stem cell markers such as Tra-1-60, Tra-1-81, ssea-1, and ssea-4 [24]. HUCMSCs have a faster doubling time in *in vitro* culture and demonstrate self-renewal ability and pluripotency [25]. Owing to higher expressions of endothelium genes FLT1, GATA4, GATA6, ISL1, LAMA1, SOX17, and SERPINA1, HUCMSCs have higher differentiation potency for endothelial generation [26]. Endothelial cells are involved in the microvascular formation and participate in hematopoietic regulation via secretion of cytokines. HUCMSCs have a variety of immunoregulatory properties, including low expression of HLA-I, no expression of HLA-DR and high concentration of immunosuppressive molecule HLA-G [27]. HUCMSCs do not express the co-stimulatory molecules CD40, 80 and 86, which are needed for the proliferation reaction of allogeneic T cells *in vitro*, suggesting low immunogenicity of HUCMSCs [28, 29]. In addition, compared with other MSCs, HUCMSCs produce

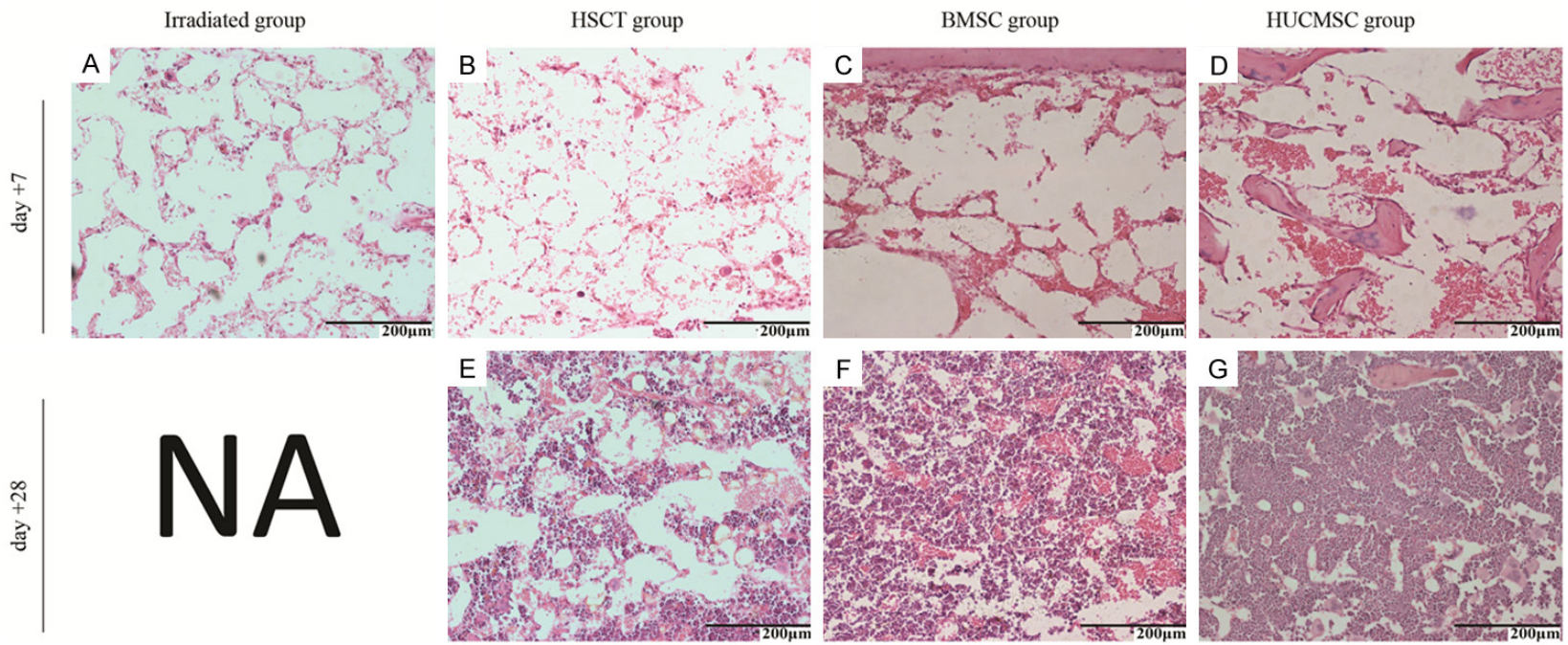


**Figure 8.** Dynamic changes in the myelogram in mice after transplantation following radiation. A. The degree of bone marrow hyperplasia in the irradiated group on day 7; B, E. Myelogram of HSCT group on days 7 and 28; C, F. Myelogram of BMSC group on days 7 and 28; D, G. Myelogram of HUCMSC group on days 7 and 28 (100×).

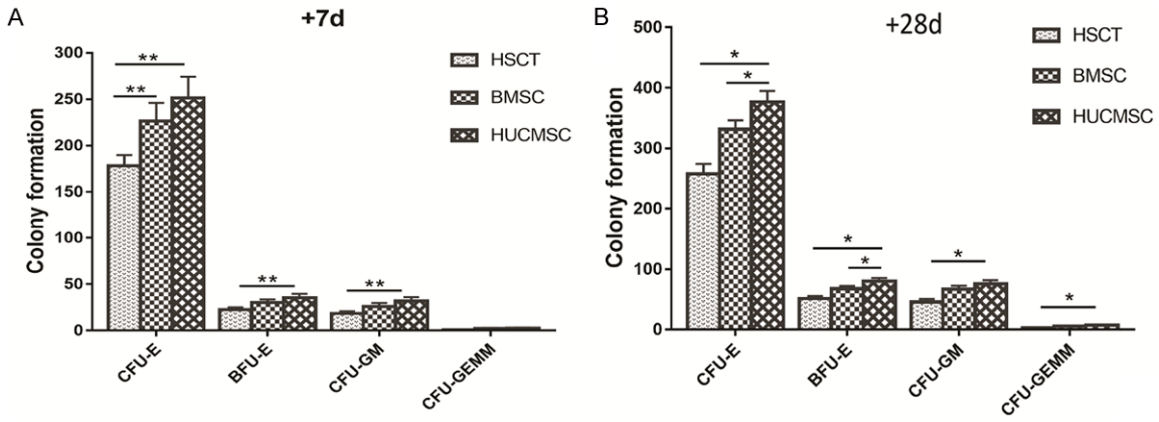


**Figure 9.** Colony formation numbers of different groups after transplantation. CB6F1 (H-2b×d) recipients were transplanted with different MSCs ($1\times10^6$) and BM cells ($1\times10^6$) from C57BL/6 donors. The HSCT group was transplanted with BM cells, HUCMSC group was transplanted with HUCBSCs plus BM cells, and BMSCs group was transplanted with BMSCs plus BM cells. On days 7 and 28, CFU-E, BFU-E, CFU-GM and CFU-GEMM colony numbers were counted. A. Histogram of colony numbers on day 7; B. Histogram of colony numbers on day 28. $^{*}P<0.05$, $^{**}P<0.01$.

**Table 1.** Colony formation after transplantation in different groups

| | +7 | | | | +28 | | | |
|---|---|---|---|---|---|---|---|---|
| | CFU-E | BFU-E | CFU-GM | CFU-GEMM | CFU-E | BFU-E | CFU-GM | CFU-GEMM |
| HSCT | 178.33±11.67** | 22.67±2.30** | 18.33±2.52** | 0.67±0.58** | 275.33±16.92 | 51.67±3.51 | 46.00±4.58 | 3.33±0.51 |
| BMSC | 226.33±19.66 | 30.00±3.61 | 26.00±3.61 | 2.33±0.58 | 331.67±14.57 | 67.67±4.51 | 67.00±5.57 | 5.33±0.53 |
| HUCMSC | 251.33±22.83 | 35.33±4.25 | 32.00±4.01 | 2.67±0.58 | 376.33±18.45* | 80.33±4.89* | 76.00±5.47* | 7.33±0.58* |

CB6F1 (H-2b×d) recipients were transplanted with different MSCs ($1\times10^6$) and BM cells ($1\times10^6$) from C57BL/6 donors. The HSCT group was transplanted with BM cells, HUCMSC group was transplanted with HUCBSCs plus BM cells, and BMSCs group was transplanted with BMSCs plus BM cells. On days 7 and 28, CFU-E, BFU-E, CFU-GM and CFU-GEMM colony numbers were counted. $^{*}P<0.05$, $^{**}P<0.01$.

G-CSF, GM-CSF, LIF, IL-1β, IL-6, IL-8, IL-11 with dramatically higher concentrations and other hematopoietic growth factors [30].

At present, MSC-based therapies have achieved certain results in the treatment of acute radiation disease, but further research is needed in terms of molecular mechanism, feasibility and safety [31]. Overall, these findings revealed that HUCMSCs exhibited a more noticeable ability to restore HIM and promote the hematopoietic function recovery in acute bone marrow radiation disease. These results displayed that HUCMSCs may contribute actively to hematopoietic reconstitution. These observations are of great significance to explore the correlation between HIM restoration and hematopoietic damage recovery and the mechanisms underneath, which probably provide a new way to search for effective treatments for hematopoietic damage.

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## Disclosure of conflict of interest

None.

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