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Parvovirus B19 Infection May Potentially Determine the Fate of Hematopoiesis by Altering the Human Bone Marrow Mesenchymal Stem Cells Differentiation

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Abstract

Background: Human bone marrow mesenchymal stem cells (hBM-MSCs), as supporters for hematopoiesis, differentiate into osteoblasts and adipocytes. Studies showed that infection of hBM-MSCs by Parvovirus B19 (B19V) can affect the differentiation capability of hBM-MSCs. This study aims to evaluate B19V effects on the differentiation of hBM-MSCs.

Materials and Methods: In this experimental study hBM-MSCs were cultured up to passage 3. Nucleofection was subsequently employed to deliver a plasmid containing the B19V genome into the cells. The transfected cells were then differentiated into osteoblast and adipocyte lineages. qRT-PCR was then performed to analyze the differentiation 14 days after transfection.

Results: On the 14th day after induction the findings demonstrated a significant increase in adipocyte-specific (PPARγ and LPL) gene expression compared to the control group ($p<0.05$) and a slight but not statistically significant decrease in the expression of the osteocyte-specific genes (RUNX2 and osteocalcin) ($p>0.05$).

Conclusion: The results suggest that B19V infection can promote the differentiation of hBM-MSCs towards adipocytes and affect the bone marrow microenvironment as well as hematopoiesis.

Keywords: Adipocyte; Bone marrow; Mesenchymal stem cell; Osteoblast, Parvovirus B19

Introduction

The human bone marrow niche has two significant cell populations consisting of hematopoietic stem cells (hBM-HSCs) and mesenchymal stem cells (hBM-MSCs) that affect hematopoiesis due to offering physical support to hBM-HSCs by adipocytic and osteoblastic differentiation (1). Therefore, hBM-MSCs provide a suitable substrate for HSC proliferation and can regulate their homeostasis (2-4).

Many studies have demonstrated that hematopoiesis requires an equal and stable balance between adipocytic and osteoblastic differentiation as negative and positive regulators, respectively (1, 5-8). On the other hand, impaired osteogenic differentiation or heightened adipocyte differentiation will likely cause osteoporosis and downregulate hematopoiesis (9-11). According to experiments, some transcription factors

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play a substantial role in osteoblastic differentiation; Runt-Related Transcription Factor 2 (RUNX2) is a chief transcription factor in the differentiation of osteoblasts (12). Also, the components of particular signaling pathways can orient and start the adipogenesis; for instance, Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) and CCAAT enhancer binding protein beta (Cebpβ) increase MSC differentiation to adipocytes (13-16).

In addition to internal factors, some infectious organisms can disrupt the hBM-MSCs differentiation balance and consequently affect hematopoiesis. One of the most critical viruses which go for bone marrow stem cells is Parvovirus B19 (B19V). Parvovirus B19 is a small and non-enveloped virus with a linear single-stranded DNA belonging to the genus Erythrovirus within the Parvoviridae family. The single-stranded genome of the virus by two surface virus capsid proteins (VP1 and VP2) and a nonstructural protein called NS1 that covalently bonds with DNA and helps replication (17, 18). B19V enters through the respiratory tract and then can infect the bone marrow microenvironment and remain latent in host cells which can stimulate cytotoxicity and upregulate the expression of pro-inflammatory cytokine as well (6, 19-21). Around the world, its infection is too common (more than 70%) and primarily asymptomatic in healthy adults (19). B19V has noteworthy tropism to erythrocyte progenitor cells (EPCs) that can enter to EPCs by P antigen (globoside) and disrupt erythrocyte production (22, 23). However, some studies have shown that B19V can infect several non-erythroid cells like hBM-MSCs (24). The present study investigated the relationship between the infection of B19V and hBM-MSCs differentiation.

Materials and Methods

hBM-MSCs isolation and culture

Bone marrow aspirates were obtained from three healthy donors who were supposed to have bone marrow-related diseases. The bone marrow mononuclear cells (BM-MNCs) were separated by using Ficoll [GE Healthcare, USA], and eventually, $1\times10^6/cm^3$ of them were transferred to T75 flasks (SPL Life Sciences, Korea). The flask contained Dulbecco's Modified Eagle's Medium (DMEM; Bioidea, USA) supplemented with 10% v/v FBS. hBM-MSC cultures were then incubated under standard conditions (37◦C, 5% CO2) for Three weeks. Culture replacement was implemented every three days, and after that, Cells were counted with Neubauer's slide by adding 50µl of 0.4% Trypan blue (Sigma-Aldrich, USA) into the same volume of the suspension that living cells did not stain with this color.

hBM-MSCs immunophenotyping

After the third passage, cells were trypsinized and added PBS solution. MNCs were stained with fluorescent isothiocyanate (FITC)-conjugated monoclonal antibodies against CD73, CD90, CD105, and CD45 [Ebioscience, USA] and then incubated at 4 ºC for 45 to 60 minutes. Afterward, BM-MNCs were centrifuged, and 100µl of 1% paraformaldehyde solution was added to the mixture. For control, instead of a FITC-conjugated antibody, an isotype control solution (Mouse IgG1) was used. Due to the low probability of contamination, some cells were frozen following a cell count; less than 100 thousand cells were frozen in a single cryotube (SPL Life Sciences, Korea). The analysis was performed by flow cytometry analyzer (FACScan; Becton Dickinson, Bedford, MA, USA).

Plasmid transformation and hBM-MSCs transfection

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pHI0 plasmid, carrying the HV strain of B19V (GenBank Accession no: AF162273) genome (a generous gift from Professor Gallinella (University of Bologna, Italy)) was introduced into electrocompetent DH5α bacteria (Thermofisher, USA) using the electroporation method. Positive colonies on Lysogeny broth (LB) agar with 100 μg/ml ampicillin (Sigma-Aldrich, USA) were incubated in LB broth medium at 37^{o}C for 16 hours. Afterward, Plasmids were isolated according to the low-copy plasmid extraction protocol [Macherey-Nagel, Germany]. Transfection was performed with 5 μg of pHI0 plasmid per 2 × 10^{6} cells via Nucleofector (Lonza, Switzerland) with the program U23. After yielding around 90% confluence, the cells were split into two different groups: The first group was transfected with pHI0 containing the B19V genome, and in the second group, pHI0 was transfected without the B19V genome as a control. The cells were then incubated under standard conditions for 36 hours.

Fluorescence microscopy

To assess transfection, Green Fluorescent Protein (GFP) was added; GFP is a vector that emits green light under the inverted fluorescent microscope (Figure. 4a). After 36 hours, the expression of GFP in transfected cells was detected by inverted fluorescence microscope (Eclipse-TE2000-E, Japan) equipped with a fluorescence filter. Digital images were captured using a camera system [Nikon, Japan] that confirmed transfection. Furthermore, VP1, VP2, and NS1 expression were detected using Real-time PCR (RT-PCR).

Osteogenic and adipogenic differentiation of BM-MSCs

After 36 hours, the supernatant medium was drained, and 1 ml of the osteoblast differentiation medium (Thermofisher, USA) was added to each well. The medium was changed twice a week for two weeks, and on the 14th day, the medium was removed, and cells were washed using PBS and fixated with 10% formalin; next, they were washed again with distilled water. Finally, cells were stained with Alizarin Red S dye 1% (Sigma-Aldrich, USA) to indicate successful osteoblastic differentiation. Alizarin Red S is a stain that can attach to calcium sediments of the calcified matrix in differentiated osteoblasts. The alkaline phosphatase (ALP) activity of osteoblasts (25) was also measured with an ELISA method [Sigma-Aldrich, USA].

Like a similar process, after 36 hours, adipocyte differentiation medium (Thermofisher, USA) was added, and on the 14th day, Oil Red O (Sigma-Aldrich, USA) staining was done. The medium was depleted, and cells were washed using PBS. After fixing with 10% formalin and washing with distilled water, 1 ml of 60% isopropanol was added, and staining was carried out. Oil Red O binds to fat droplets, and differentiation is confirmed if the specific lipid vesicles are present. Additionally, ALP activity was measured with p-nitrophenyl phosphate (Sigma–Aldrich, USA) according to the manufacturer's instruction.

Target gene analysis

On the 14th day, total RNA was extracted from differentiated infected cells using Trizol (TRI Reagent, Sigma), and RT-PCR (Qiagen, USA) was performed in microtubes using random hexamers [Eppendorf, Germany]. The expression of RUNX2 and osteocalcin for osteoblast and PPARγ and LPL for adipocyte differentiation were checked by PCR (Eppendorf, Germany)by the following primer pairs: RUNX2 forward: GCCTTCAAGGTGGTAGCCC, RUNX2 reverse: CGTTACCCGCCATGACAGTA, osteocalcin forward: GCAAAGGTGCAGCCTTTGTG, osteocalcin reverse: GGCTCCCAGCCATTGATACAG, PPARγ forward:

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TCGTGGTACTTTACGCCTCG, PPARγ reverse:
TGGTCATTTCGTTAAAGGCTGA, LPL forward:
AGGAGCATTACCCAGTGTCC, LPL reverse:
CCAAGGCTGTATCCCAAGAG; to optimize annealing temperature. Afterward, electrophoresis was done for reaction products with 2% agarose gel, and the bands were photographed using Gel Documentation System [Sabz, Iran].

In the next step, the expression of these genes was evaluated with Real-time PCR [ABI, Belgium] performed by synthesized cDNA. Quantitative real-time PCR (qRT-PCR) was conducted in duplicate by SYBR Green Master Mix (2X) containing Hot Start Taq polymerase. The cycle threshold (Ct) was calculated and normalized against β-actin as an internal control.

Statistical Analysis

All statistical analyses were carried out using GraphPad Prism software v.7.0. Unpair t-test was used for data analysis. The results were presented as means ± SD and $p<0.05$ was determined for statistical significance analysis.

Ethical Consideration

Human ethics approval was obtained from the Research Ethics Committee of Qazvin University of Medical Sciences (ethical approval code: IR.QUMS.REC.1395.191).

Results

hBM-MSCs differentiation and immunophenotyping analysis

Morphology and biomarkers of hBM-MSCs cultured were identified by light microscopy (Figure Ia). Furthermore, in flow cytometric analysis, positive CD73, CD90, CD105, and negative CD45 were detected, which confirms the existence of hBM-MSCs (Figure Ib). As mentioned above, the adipogenic and osteogenic differentiation of transfected hBM-MSCs was performed by Oil Red O and Alizarin Red S staining, in which there a higher adipogenic differentiation (Figure IIa) was compared with their control group (Figure IIb). Contrary to adipogenic differentiation, there was no osteogenic differentiation (Figure IIc, IId). This was confirmed by measuring the ALP activity of the osteogenic medium transfected cells with the ELISA kit, which showed no significant difference in the studied groups (Figure III).

The efficiency of hBM-MSCs transfection

Thirty-six hours after hBM-MSCs transfection, the expression of NS1, VP1, and VP2 was evaluated by RT-PCR using HR1, HR3, and HR4 primers, respectively. The NS1, VP1, and VP2 proteins were present in transfected cells on the mRNA level, meaning the hBM-MSCs were correctly transfected. Also, an image of the gel was captured, establishing the virus's activity within hBM-MSCs (Figure IVb).

Adipogenic and osteogenic gene expression

On the 14th day after induction, the expression of RUNX2 and osteocalcin genes of both transfected and control cells showed slight decrease which was not significant (Figure Va), which indicates osteoblastic differentiation. On the other hand, on the day 14 after transfection, there was a significant increase in adipocytic genes, including PPARγ and LPL, of both transfected and control cells ($p<0.05$) (Figure Vb).

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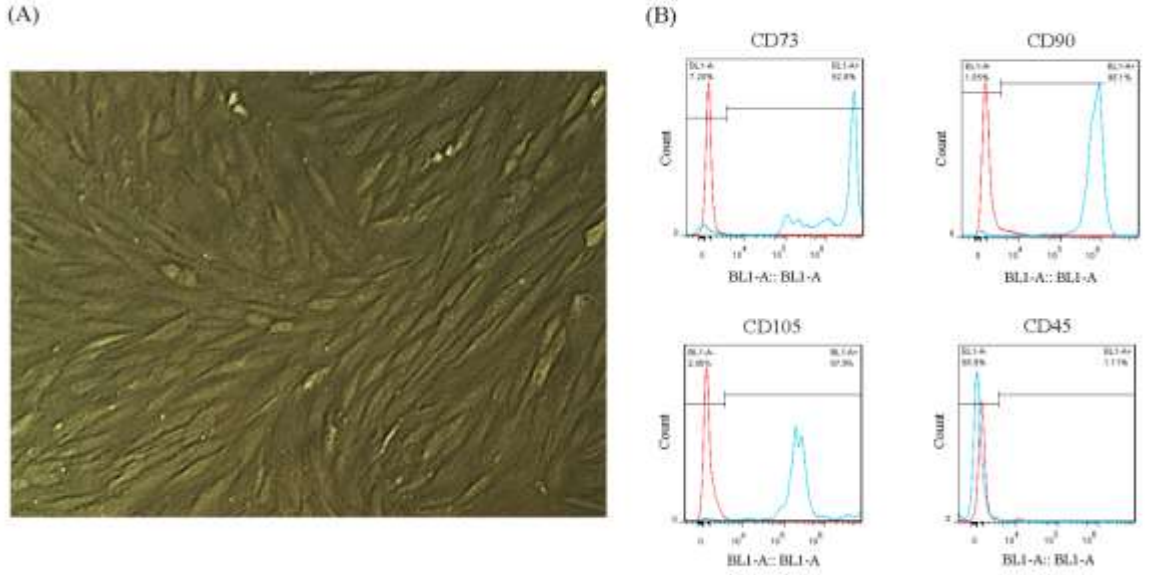

Figure 1**.** The confirmation of isolated mononuclear cells as hBM-MSCs. A Morphology of passage three hBM-MSCs obtained from bone marrow aspirate. Cultured hBM-MSCs display spindle-shaped morphology, which was identified using light microscopy. **b** Expression of surface markers in BM-MSCs. hBM-MSCs were positive for CD73, CD90, CD105 (> 90%) and negative for CD45 (< 5%).

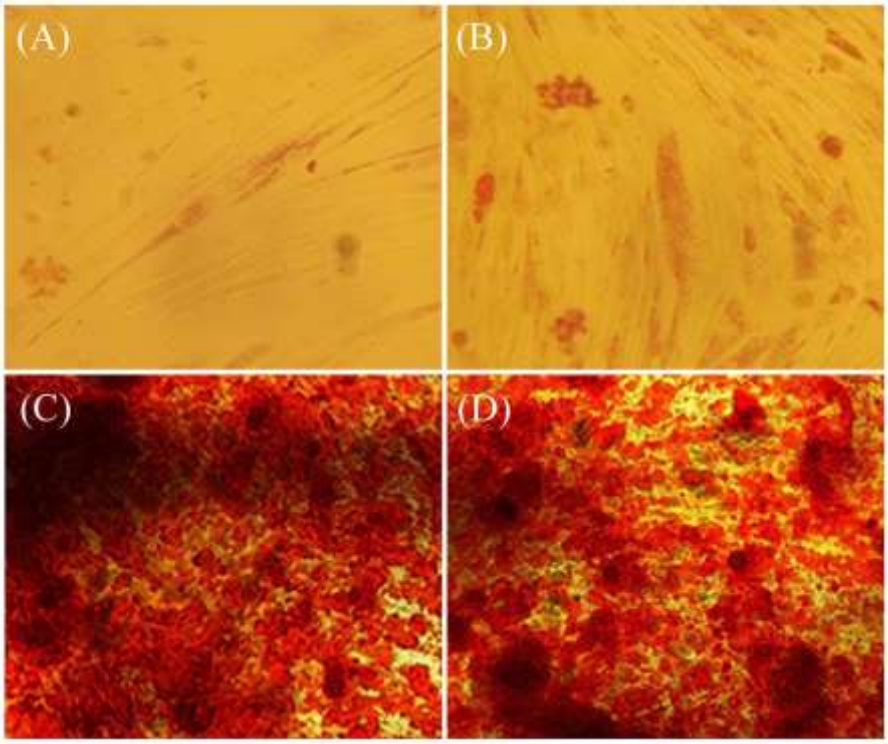

Figure 2. Alizarin Red S and Oil Red O staining of transfected hBM-MSCs on day 14 after transfection. Transfected cells had a higher adipogenic differentiation (a) compared with their control group (b). There was no differentiation in the osteogenic differentiation medium of transfected hBM-MSCs (c) and their control (d).

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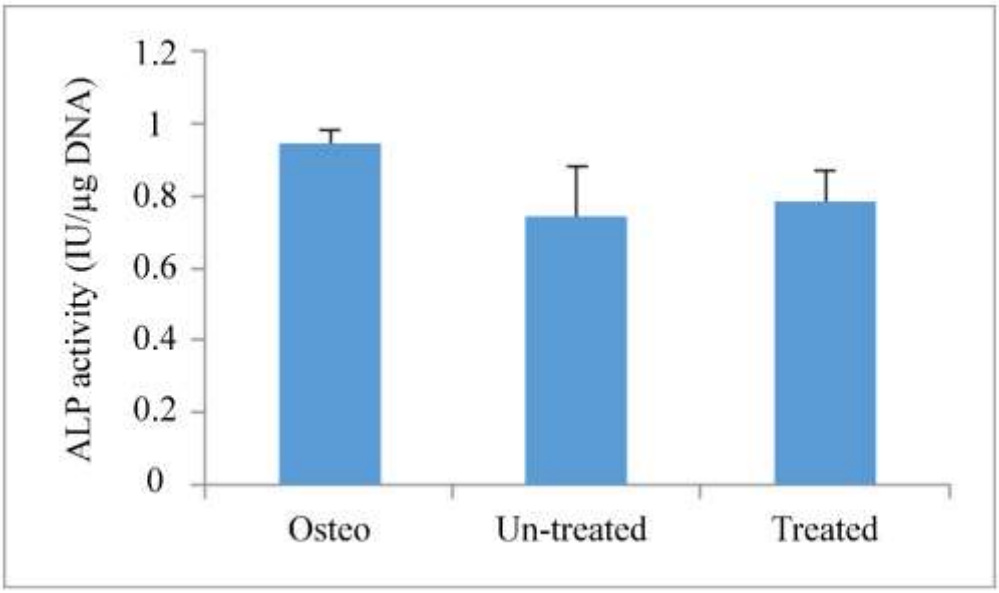

Figure 3. Measuring the ALP 14 days after transfection. hBM-MSCs differentiation to osteoblasts shows no significant increase in the ALP activity of differentiated cells.

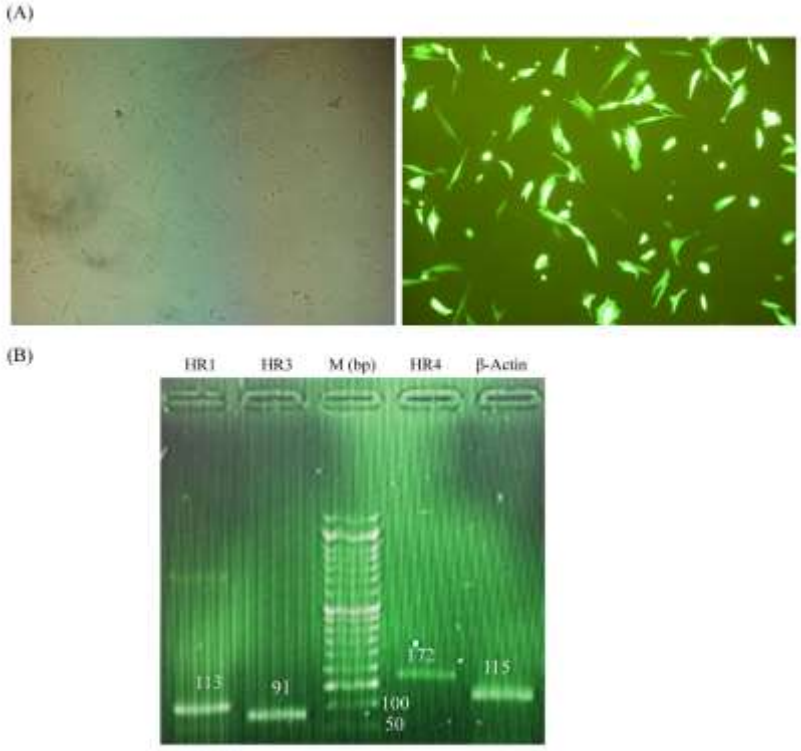

Figure 4. a. To evaluate the transfection efficacy, a few hBM-MSCs were transfected by a GFP vector, and the emission of green light under an inverted fluorescent microscope after 36 h of transfection indicates a successful hBM-MSCs transfection. b. Validation of gene expression in transfected cells by RT-PCR containing HR1, HR3, and HR4 primers which encode NS1 and capsid proteins of B19V, respectively. The β-actin gene was used as an internal control.

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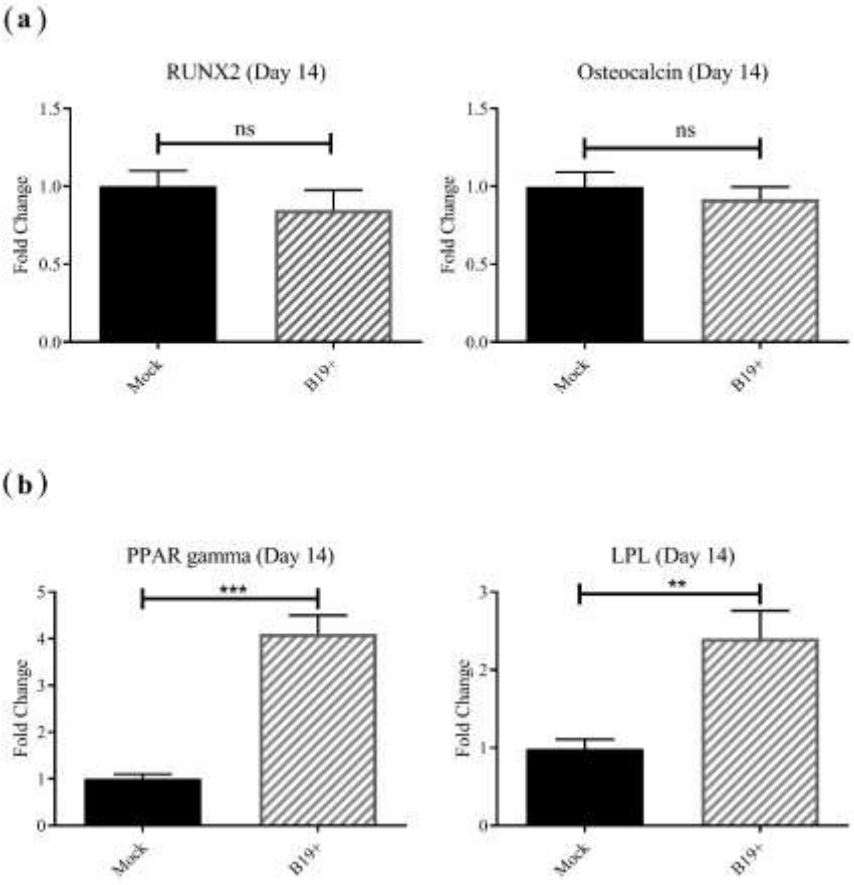

Figure 5. Expression patterns of osteogenic and adipogenic genes of B19V-transfected hBM-MSCs and controls on the 14th day after transfection **a.** There were not any significant alterations in expression levels of RUNX2 and Osteocalcin genes ($p>0.05$). **b.** The expression of PPAR-γ and LPL genes significantly increased ($p<0.05$). Gene expressions of transfected hBM-MSCs were normalized to control groups. Asterisks show statistically significant changes.

Discussion

Viruses are one of the most essential factors in developing malignancies, especially hematological ones, to the point that more than 20% of cancers are correlated with oncogenic viruses (26). B19V is the only human-infecting virus in the Parvoviridae family that causes hematological manifestation in patients. According to some studies, prolonged B19V infection may stimulate the production of inflammatory cytokine-affected cells and thus can influence hematopoiesis (27). The most important disease created by B19V in individuals with defective immune systems is aplastic anemia. Also, B19V can infect hBM-MSCs, potentially leading to unfavorable effects on hematopoiesis (28).

In a study by Fritch Lilla et al., a high load of B19V was reported in acute lymphoblastic leukemia patients (29). Ibrahem et al. also proposed a correlation between B19V infection and acute leukemia (30). The final results demonstrated that the B19V-transfected hBM-MSCs tend to differentiate into adipocytes rather than osteoblasts. The

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results also indicated that there were not any significant changes in RUNX2 and osteocalcin gene expression compared to control groups, despite a slightly decreased expression. Similarly, the results were corroborated by a study conducted by Azadniv et al. in which hBM-MSCs of normal and AML-inflicted patients were isolated, and their differentiation characteristics were examined (31). In this study, no osteogenic differentiation was observed. However, adipogenic differentiation of hBM-MSCs in AML patients was evident. On the other side, in the present research, PPARγ and LPL in the adipogenic differentiation medium significantly increased. In that case, the progressive adipose tissue accumulation in bone marrow could impair hematopoiesis. In another study by Lacey et al., it was shown that the inflammatory cytokines, such as IL-1β and TNF-α, cannot shift the hBM-MSCs into osteoblasts (32); in other words, these cytokines can suppress the osteogenic differentiation and ALP activity, and RUNX2 and osterix expression.

Conversely, Amiri et al. also showed that B19V infection could significantly increase the expressions of pro-inflammatory cytokine in infected hBM-MSCs (19), and this circumstance suppresses the differentiation of osteoblasts, exacerbating the situation. This differentiation bias may negatively impact hematopoietic recovery after a bone marrow transplantation. Regarding the effect of viruses on MSC differentiation, Cotter et al. demonstrated that treating MSCs with HIV-positive serum can increase adipogenic differentiation (33). A limitation of this study is that the investigation is based on the mRNA expression level of the target genes in the transfected MSCs. The assessment of these cytokines at the protein level may provide further support to the hypothesis that B19V-infected hBM-MSCs could disrupt the bone marrow niche as well as hematopoiesis.

Conclusion

This study concluded that the infection of hBM-MSCs with B19V increases adipogenic differentiation. The upregulation of some critical genes of adipogenic differentiation in B19V-infected MSCs might affect the bone marrow microenvironment and hematopoiesis. Although more investigations are required for an insightful understanding of the relationship between B19V and hematopoiesis, molecular assays are highly recommended prior to doing any therapeutic process or stem cell therapy.

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Conflict of interest

The authors declare no conflict of interest.

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