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Research Article

Investigation of the Apoptotic Effects of Mesenchymal Stem Cells on KG-1 Leukemic Cell Line

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Abstract

Background: Mesenchymal stem cells (MSCs) are undifferentiated cells with the ability of multipotency, pluripotency, and self-renewal. MSCs show great promise in cancer therapy due to their unique features. MSC secrete various cytokines with multifunctional properties, although their roles are unclear.

Methods: We have investigated the influence of secreted cytokines from MSCs on KG-1 cells as a cell model of acute myeloid leukemia (AML). For this purpose, following the culture and characterization of MSCs, a trans-well system was used for co-culturing MSCs and KG-1. To determine apoptosis induction Ki/Caspase-3 assay was conducted for cultured KG-1 alone and in co-culture with MSCs (10:1) on day 7. In the following step, the protein was isolated from both groups (control and experimental) and western blotting was done for investigating the BAX and BCL-2 proteins expression.

Results: It was found that MSCs significantly enhanced caspase-3 activity in KG-1 cells ($P<0.05$). Besides, A significant increase in protein expression of BAX was detected, while BCL-2 displayed a dramatic reduction ($P<0.01$).

Conclusion: As a concluding remark, MSCs have a contributory role in the apoptosis of KG-1 cells that is mediated by Caspase-3, BAX, and BCL2 expression.

Introduction

Mesenchymal stem cells (MSCs) are undifferentiated multipotential cells and are capable of giving rise to diverse cell lineages, including adipocytes, osteocytes, chondrocytes, neuron-like cells, and virtually all connective tissues.[1] MSCs are most typically isolated from adult human tissues such as bone marrow, amniotic fluid, amnion, placenta, adipose tissue, and importantly from vital organs like the heart, liver, kidney, and so on.[2] Due to unique properties like self-renewal, high plasticity, regenerative capacity, and relatively non-immunogenic traits, MSCs are possibly responsible for MSC-based modulation in cell and organ transplantation. In this context, MSCs are used to cure some diseases, including neurodegenerative disorders, cardiovascular events, ischemic strokes, bone/cartilage diseases, immune-related diseases, blood disorders, cancer, and genetic disorders.[3] Amongst the listed diseases, MSC transplantation has gained more attention for hematological abnormalities.[4-6] Several lines of studies investigated the application of bone marrow-derived MSCs (BM-MSCs) for transplantation. In addition, it was reported that BM-MSCs could favor tumor growth either by enhancing tumor cells' invasive abilities or by protecting them from recognition by immune cells. Meanwhile, the risks associated with MSC-based modalities are still unclear, especially for patients with pre-existing cancers.[7] Cellular interaction between cancer cells and MSCs plays a fundamental role in promoting tumor growth and invasion.[8] In this context, cancer cells may modify the molecular content of BM-MSCs as stromal cells during tumor development, thereby affecting the properties of cancer cells. Indeed, bidirectional crosstalk of BM-MSCs with tumor cells has a crucial role in tumor progression and invasion, creating a supportive microenvironment named tumor niche.[9] The fibroblast, as part of the normal stroma, secretes an extracellular matrix (ECM), which provides a natural barrier to the progression of tumors. Notably, MSCs can play an essential role in these processes. Multiple studies have shown that MSCs can be derived from tumor-resident stromal progenitor cells.[10] Intriguingly, the migration of MSCs into damaged tissues is mediated by chemotactic gradients of cytokines secreted by the same damaged tissues.[11]

On the other hand, others have reported the opposite.[12]

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Several studies have examined how MSCs affect cell proliferation, growth, and apoptosis rates of cancer cell lines.[13] In this regard, Zhang *et al.*[14] reported that co-culturing MSCs with chronic myeloid leukemia (CML)-derived cells from the BM of CML patients could produce considerable levels of IFN-α, thereby suppressing the growth of CML cells. Likewise, Fonseka *et al.*[15] showed that umbilical cord blood-derived MSCs inhibit the proliferation of the CML cell line (K562) through G0/G1 arrest, up-regulation of the level of IL-6/IL-8 secretion and latency-associated peptide (as part of the latent TGFB complex). Meanwhile, it was found that BM-MSCs could suppress immune activity by secreting soluble cytokines.[14] Yet, little is known about the effect of the type and quantity of growth factors and cytokines secreted by BM-MSCs and the mechanisms behind it. Most of the studies have revealed how MSCs affect cancer cells.

In contrast, Paino *et al.*[16] investigated the effects of cancer cells on the differentiation of adipose tissue-derived MSC. As evidenced by *in vitro* and *in vivo* studies, MSCs cannot differentiate in the presence of cancer cells and do not assist in tumor angiogenesis, respectively. These results open interesting new scenarios in the relationship between cancer and stem cells. These findings may also lead to greater caution when managing grafts in cancer patients. With these explanations, greater caution may also be required when handling grafts in patients with cancer.[11] Also, the effects of secreted cytokines from BM-MSCs on the CML cell line (K562 cell line) were previously reported by Fathi *et al.*[17], but these effects were not investigated on the AML cell line. In light of these explanations, the purpose of this study was to elucidate the effects of BM-MSCs on the proliferation ability and apoptosis of KG-1 cells as a cell model of acute myeloid leukemia (AML). This objective was achieved by cultivating KG-1 cells alone and co-culturing KG-1 cells with BM-MSCs (10:1), and analyzing the Ki/caspase3 expression levels using flow cytometry.

Methods

Cell culture

KG-1 and BM-MSCs cell lines were provided by Pasteur Institute and Royan (Tehran, Iran), respectively. The KG-1cell and BM-MSCs cells were cultivated at RPMI (Gibco Co. UK) and low glucose-DMEM containing 10% fetal bovine serum (FBS) (Gibco Co. UK), respectively.[18]

Characterization of MSCs

To characterize the surface marker of BM-MSCs, flow cytometry analysis was performed as previously described by Adibkia *et al.*[19] To accomplish this, 1×10^6 BM-MSCs/well at passage 4 were harvested and stained with antibodies against CD34 (sc-74499), CD56 (sc-7326), CD44 (sc-7297), and CD90 (sc-53116) with incubation of 30 minutes at 4°. Following the staining process, the cells were washed with PBS containing 3-5% FBS and analyzed by FACS for the determination of cell surface markers.

Co-culture of BM-MSCs and KG-1cell line

After 4-6 passaging, BM-MSCs were cultured at a seeding density of 2×10^5 cells/well into a trans-well insert with a pore size of 0.4 µm (SPL Life Sciences Co, South Korea, Cat: 37306). After incubation of 12-16 hours, the lower wells of the trans-well plates were cultures with 1×10^6 KG-1 cells/well. This method formed two groups of cell population; a control group composed of KG-1 cells alone and the co-culturing group containing KG-1 and BM-MSCs (at a ratio of 10:1) as the experimental group. To this end, co-cultured KG-1 cells alone and co-cultured with BM-MSCs on day 7 were subjected to subsequent analysis, including protein expression of BAX/BCL2 and caspase-3.

Determination of Ki-67 and caspase-3 expression using flow cytometry

Caspases are cysteine proteases that serve a critical regulatory role in apoptosis. Caspases are typically found as inactive precursors in healthy cells but become activated upon autolytic cleavage. As a result of caspase cleavage at one or two specific sites, their substrates can be activated, inactivated, remodeled, or relocalized. Many caspase-cleaved fragments persist intact during apoptosis, which is detectable by flow cytometric analysis using substrate-specific antibodies. To determine how BM-MSCs affect the proliferation and apoptosis of the KG-1 cells, ki/caspase-3 expression was investigated. For this purpose, the KG-1 cell line was co-cultured with BM-MSCs for 7 days. At the end of co-culture time, the Ki-67 proliferation assay was conducted by harvesting and washing the cells with PBS. Afterward, the cells were exposed to 0.2% Triton X-100 for 15 min, followed by staining with antibody solution containing 5 µl of PE Mouse Anti-Ki-67 (Cat No:556027), incubating for 30 min, and subjected to flow cytometric analysis.

Likewise, for the determination of caspase-3 activity, KG-1 cells were collected and washed twice with PBS supplemented by 5% FBS. Then, the cells were fixed by incubating with FCM fixation buffer for 30 min (sc-3622, Santa Cruz, CA), followed by washing and permeabilizing with FCM permeabilization buffer (sc-3623, Santa Cruz, CA) with incubation of 5 min at RT. After washing cells, FITC Active Anti-caspase-3 conjugated (Cat No:550480, BD Bioscience, Belgium) was added to the cells for 30 minutes. Flow cytometry was performed to analyze the caspase-3 expression.[20]

Analysis of BAX and BCL2 protein expression using Western blot assay

For the assessment of protein expression, 2×10^6 KG-1 cells/well were harvested, washed twice in cold PBS, and lysed with RIPA buffer at 4°C for 30 min. In the following, homogenates were centrifuged at 13000×g for 15 minutes at 4°C. The concentrations of proteins were determined by the BCA protein assay kit (Pierce, Rockford, IL, USA). Subsequently, 50 µg of protein sample was loaded on 12% SDS-PAGE. After the separation of proteins on a polyacrylamide gel, proteins were transferred to PVDF membranes. To prevent nonspecific interaction of proteins in the membrane, the membranes were blocked by TBS-T buffer (20 mM Tris-HCL, 137 mM NaCl and 0.1% Tween 20) supplemented with 5% skim milk and incubated for

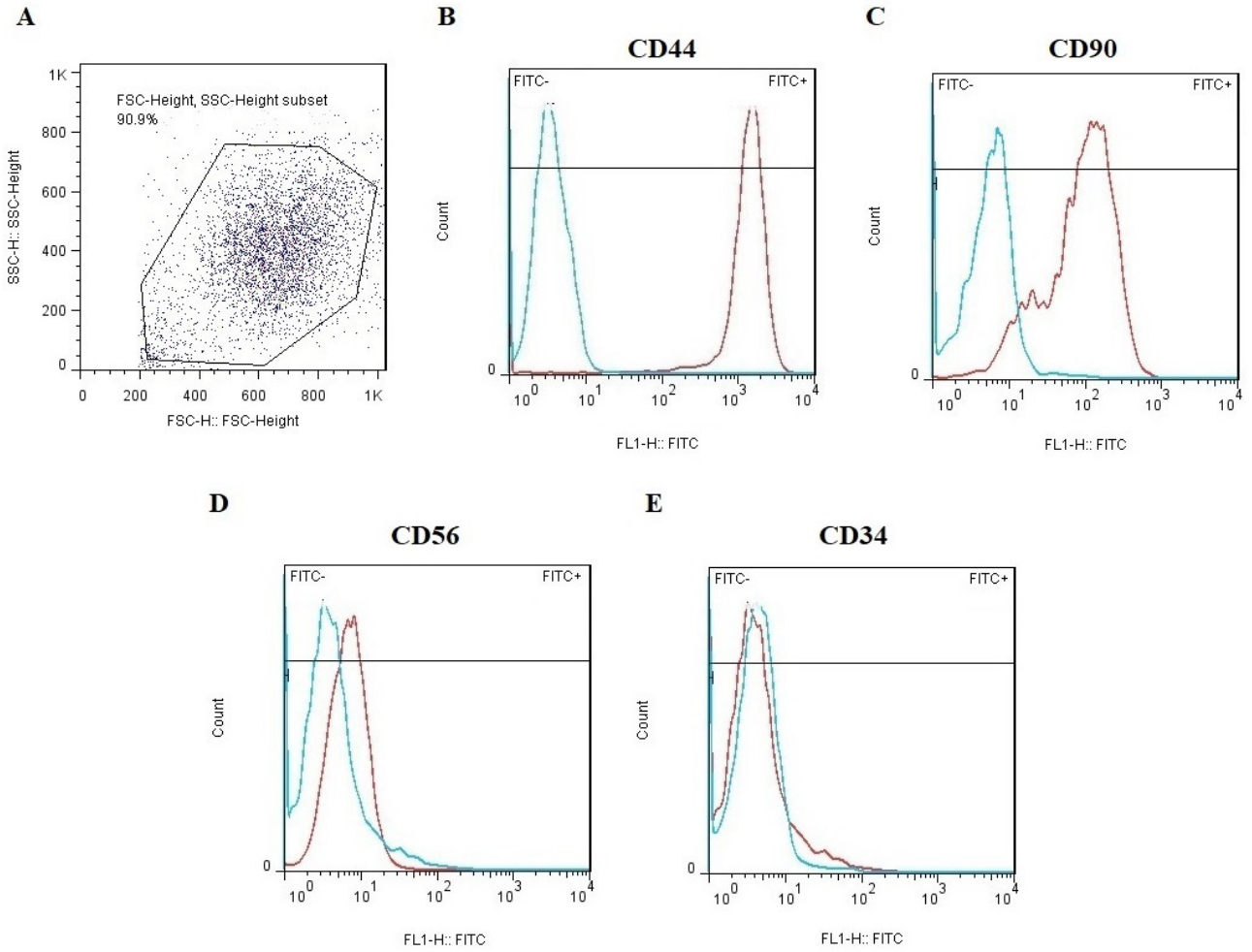

Figure 1. Flow cytometric analysis to determine cell surface markers of BM-MSCs. In this experiment, individual cell surface markers were examined by separate cell populations, and isotope controls served as negative controls. Part A shows a total population of cells; The BM-MSCs were expressing CD44 (B) and CD90 (C) while they were negative for CD56 (D) and CD34 (E). Also, the blue histogram represents isotype control. Acquired flow cytometry data were assessed using FlowJo software (version 6.2).

60 minutes at 25 °C. Thereafter, the membranes were incubated with primary polyclonal antibodies against targeted proteins at 4°C overnight as follows: β-actin (sc-47778), BAX (sc-20067), and BCL-2 (sc-7382). Following two washes with TBS-T, the membranes were exposed to TBS-T containing goat anti-mouse secondary antibody at a dilution of 1:5000 (Santa Cruz) for 60 min at 25 °C. Finally, after washing the membranes, the protein bands were visualized by enhanced chemiluminescence procedure (Roche, UK) using X-ray film. ImageJ 1.6 software was used to calculate each protein band's signal intensity, which was then normalized to respective β-actin control.[21-23]

Statistical analysis

All obtained results were compared with t-test comparison assay. P<0.05 was set as statistically significant by Graph Pad Prism version 6.01.

Results

Immunophenotypic analysis of BM-MSCs

The expression profile of cell surface markers of the BM-MSCs is depicted in Figure 1. The results showed that BM-MSCs expressed CD44 and CD90 as mesenchymal markers, but did not express hematopoietic markers such as CD56 and CD34.

BM-MSCs decreased the viability of KG-1 cells through caspase-3 activity

A significant inhibitory effect of BM-MSCs on KG-1 cell proliferation was determined by Ki-67 expression as a proliferative surface marker (Figure 2). After 7 days of co-culturing of KG-1 with BM-MSCs, the percentage of Ki-67 dramatically decreased to7.41% (**P<0.01) compared to KG-1 alone (97.3%) (Figures 2C-E). This result indicates the inhibitory impact of BM-MSCs on KG-1 cells. Furthermore, caspase-3 was assessed in co-cultured KG-1 cells with BM-MSCs to determine whether BM-MSCs induce caspase-3 activity. As observed in Figure 2H-J, there was a significant increase in the level of caspase-3 in co-cultured cells compared to the control ones (*P<0.05), addressing the effect of BM-MSCs in promoting caspase-3 activity.

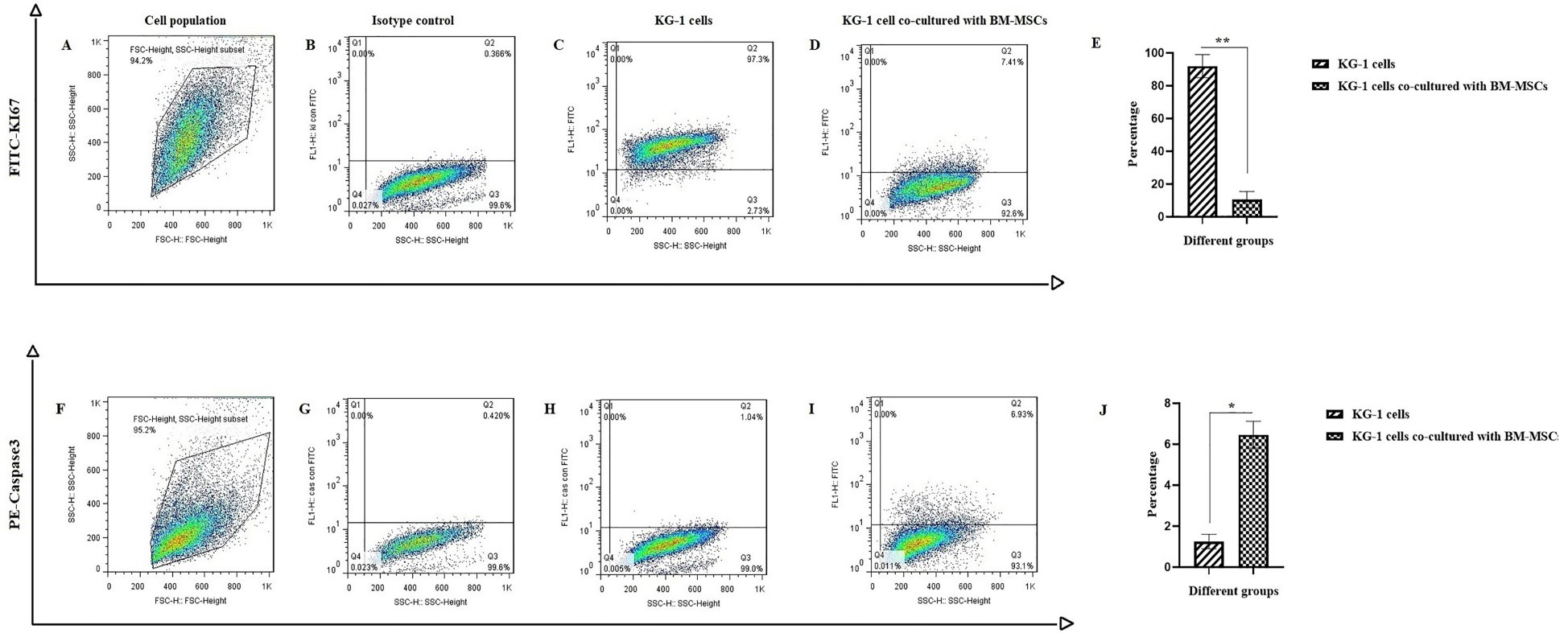

Figure 2. Proliferation and apoptosis determination in co-cultured KG-1 cells with BM-MSCs. Flow cytometric analysis was conducted to determine the proliferation and apoptosis of the cells using Ki-67 and the caspase-3 levels. The upper part shows the Ki-67 marker, and the lower part displays the caspase-3 expression. Panels A and F point to the selected cell populations; Panels B and G depict isotype control groups; Panels C and H show KG-1 cells alone, and D and I represent co-cultured cells. The percentage of cells expressing Ki-67 and the caspase-3 were displayed in parts E and J. Data are expressed as mean ± SD from three independent experiments (**P*<0.05 and ***P*<0.01).

BM-MSCs could alter BAX and BCL-2 protein expression in KG-1 cells

Western blotting analysis was carried out to determine the effect of BM-MSCs on the expression of pro- and anti-apoptotic proteins. For this purpose, the expression level of pro-apoptotic BAX and anti-apoptotic BCL-2 was measured. Figure 3 shows a significant increase and decrease in BAX and BCL-2 protein levels, of about 3.67 and 0.63 folds, respectively (***P*<0.01). Moreover, co-cultured cells exhibited an increase in BAX/BCL-2 ratio by 5.78 folds (*****P*<0.0001).

Discussion

Cancer is one of the leading causes of morbidity and mortality worldwide. Several therapeutic options are available to treat cancer, including chemotherapy, radiotherapy, and surgery. However, these approaches are often correlated with multidrug resistance, recurrence of metastasis, and frequent off-target effects. Considering this explanation, stem cell-based therapy has drawn significant attention in the field of cell-based therapy.[24] Stem cells are a population of undifferentiated cells with the capability of self-renewal,

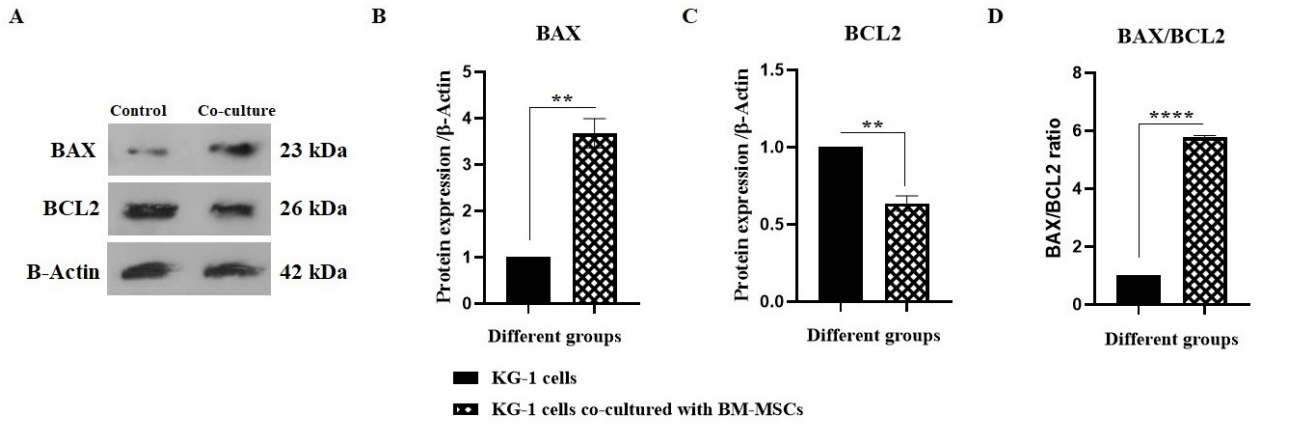

Figure 3. The impact of BM-MSCs on apoptotic-related proteins. Representative western blotting was depicted in part A. The expression level of BAX and BCL2 was detected by western blot-assisted analysis (B and C). Bax/Bcl-2 ratio was shown in part D. The data are expressed as the mean±SD from three independent experiments. ***P*< 0.01 and *****P*< 0.0001.

differentiation into diverse cell types, and proliferation to form a clonal population from a single cell.[25] In general, stem cells are categorized into somatic stem cells (adult stem cells) and embryonic stem cells (ESCs). A variety of cells can be differentiated from adult stem cells, including hematopoietic stem cells (HSCs), MSCs, endothelial progenitor cells (EPCs), neural stem cells (NSCs), and other cell types.[26] MSCs are the most commonly used cells in stem cell-based therapies. Indeed, MSC is a pluripotent cell that can differentiate into bone, fat, cartilage cells, etc. In this regard, MSCs-derived tissues can be employed as a novel therapeutic intervention in various fields, such as regenerative medicine, tissue engineering, grafting, remodeling of scars, and functional recovery.[27] A variety of diseases can benefit from cell-replacement therapy, including progressive neurodegenerative disorders, inflammatory bowel disease, respiratory diseases, spinal cord injuries, liver disease, stroke or trauma, bone disease, diabetes, chronic wounds, and so on.[28] The ability of stem cells to target primary and metastatic tumor foci makes them innovative delivery platforms.[29] In preclinical animal models, engineered stem cells can stably express bioactive factors and decrease tumor volume.[30] It is well documented that MSCs can inhibit tumor growth, as evidenced by *in vitro* and *in vivo* studies. Relying upon this, Secchiero *et al.*[24] found that BM-MSCs could hinder tumor growth in immunodeficient mice models of disseminated non-Hodgkin's lymphomas xenografts, indicating anti-lymphoma activity of BM-MSCs. A further study showed that stem cells derived from the umbilical cord matrix completely mitigated rat mammary adenocarcinomas without evidence of metastases or recurrences.[31] It has also been reported that adipose tissue-derived-MSCs (ADSCs) exhibit anti-tumor and anti-proliferative effects. In this context, Cousin *et al.*[32] provided evidence that intra-tumoral administration of ADSC impeded tumor growth and provoked pancreatic cancer cell death in a model of pancreatic adenocarcinoma. According to Yang *et al.*[33], ADSCs suppress cell proliferation and tumor growth in human U251 glioma cells *in vitro*.[33] In addition, they found that conditioned media of adipose-derived MSC inhibited the growth of multiple tumor cell lines, including the A549 cell line, as a model of lung cancer, the HT29 cell line, as a model of rectal cancer, and the MCF-7 cell line as a model of breast cancer.[33] Despite the superior anti-tumor impact of MSCs, contradictory information has also been reported. In this regard, MSCs-derived connective tissues and the bone marrow create a supportive microenvironment for normal and leukemic hematopoietic cell populations to grow, survive, and differentiate.[34] It has also been reported that specific soluble mediators released by BM-MSCs have a crucial role in chemoresistance and leukemogenesis.[35] A study by Sun *et al.*[36] found that BM-MSCs promote tumor angiogenesis and proliferation of melanoma cells. As a matter of fact, several growth factors and cytokines produced by MSCs play a substantial role in modulating cancer cells. Therefore, this study determined whether BM-MSCs could impact KG-1 cell apoptosis. Apoptosis is commonly quantified by Ki/caspase-3 expression. Notably, identifying how MSCs-secreted cytokines and growth factors induce cell damage/death is essential for evaluating the biological response to cell-based therapy. Based on these findings, it can be declared that MSCs exhibit inhibitory impacts on KG-1 cells as a model of AML. This inhibition may be possibly attributed to the downregulation of Ki-67 and the upregulation of the caspase-3 level. However, it is still unclear how factors such as cytokines affect the survival rate of leukemic cells. Therefore, further investigations are in demand to elucidate cytokine and chemokine array. There was also evidence that concurrent upregulation of BAX with downregulation of BCL-2 level induce apoptosis. These results are in accordance with previously published results regarding the association of BAX overexpression with a reduced level of BCL2 protein expression.

Conclusion

Based on the current evidence, there is still no clear picture of how MSCs affect cancer cells. It can be attributed to the contradictory roles of MSCs in terms of either favorable or unfavorable effects on the growth of cancer cells. MSCs and tumor cells are influenced by various factors, such as

membrane fusions, metabolites, and growth factors, which can complicate their cellular interplay. In light of this, MSCs should be applied with more caution in patients with a history of cancer. Considering all these explanations, the results of the current study indicated that BM-MSCs significantly induced apoptosis in AML cells. MSC-secreted cytokines appear to inhibit tumor cell proliferation through BAX/BCL2 and caspase-3 cascades. Further research is needed to identify other agents that may contribute to the anti-proliferative properties of BM-MSCs.

Ethical Issues

Ethical consent was approved by an ethics committee at Tabriz University of Medical Sciences, Tabriz, Iran (Ethic Code No: IR.TBZMED.VCR.REC.1399.131).

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Author Contributions

Raheleh Farahzadi: Conceptualization, Methodology, Formal Analysis, Investigation. Behnaz Valipour: Investigation. Zohreh Sanaat: Investigation. Ali Akbar Movassaghpour-Akbari: Investigation. Ezzatollah Fathi: Supervision, Writing - Review & Editing, Soheila Montazersaheb: Supervision, Writing - Review & Editing.

Conflict of Interest

The authors report no conflicts of interest.

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