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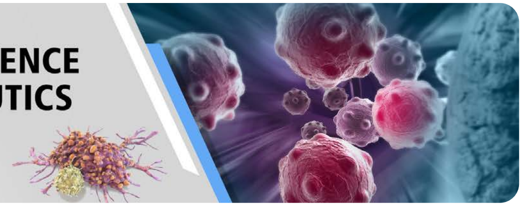
Research Article



Potential Role of Mesenchymal Stem Cells in Acute Myeloid Leukemia

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Abstract

Background: Mesenchymal stem cells, MSCs, can be found in bone marrow and other tissues. Acute myeloid leukemia, AML, is a kind of cancer that mostly affects the blood and bone marrow. It is distinguished by the aberrant myeloid cells growing rapidly. To what extent MSCs are altered in AML and to what extent they contribute to altered niche effects are underexplored.

Aim: In order to shed light on their interaction and their therapeutic uses, we aimed to characterize the MSCs and study the similarities and differences between AML patients and healthy controls.

Methods: MSCs used for this study were obtained from 6 AML patients and 10 healthy controls after signing the consent form. Isolated MSCs were characterized using flow cytometry for surface markers, and then apoptosis, proliferation, potency, and differentiation potential were evaluated.

Results: MSCs from AML and control were successfully isolated and characterized, expressing cell surface markers (CD105, CD90, CD146) and intracellular STRO1 protein. Moreover, our data showed that AML-MSCs had lower apoptosis, higher potency, higher proliferation, and higher osteogenesis and adipogenesis compared to control-MSCs.

Conclusion: Our data suggest that AML-MSCs might induce /maintain blast proliferation, confer AML-blast resistance to chemotherapy through reduced apoptosis, and might lead to a hostile bone marrow microenvironment. The potential of MSCs in the treatment of AML is an active area of research. In order to develop more effective treatment plans, we think that better understanding AML-MSCs' role in the pathophysiology of AML will come from defining them.

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Introduction

Acute myeloid leukemia (AML), is a type of cancer that affects the myeloid cells, which are responsible for producing red blood cells, platelets, and certain white blood cells [1-3]. It is a rapidly progressing disease characterized by the uncontrolled growth of abnormal myeloid cells in the bone marrow and blood. Although the precise cause of AML is still unknown, a number of risk factors have been found. There's been evidence linking elevated radiation exposure and specific chemical exposures, including benzene, to a higher chance of AML development [1-3]. Additionally, there is an increased chance of developing this disease in those who have specific genetic abnormalities,

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such as Fanconi anemia and Down syndrome [1-3]. AML arises from genetic mutations in the myeloid cells, leading to abnormal proliferation and impaired differentiation (3-8). Genes involved in signaling cascades, DNA repair, and cell cycle regulation are frequently impacted by these mutations [3-8]. The growth of leukemic cells is aided by the accumulation of these genetic abnormalities, which interfere with normal hematopoiesis [3-8]. In AML, a number of recurrent genetic mutations have been found. Mutation of the tumor suppressor gene, *TP53*, is associated with abysmal survival outcomes in AML [3-8]. The mutations in the *c-KIT*, were associated with poor prognosis in AML patients [3-8]. The *FLT3* gene, which codes for a receptor tyrosine kinase essential to cell growth and survival, is one frequently occurring mutation [3-8]. Another gene that is often altered is *NPM1*, which is involved in the transport and synthesis of ribosomes [3-8]. The microenvironment of the bone marrow is also essential to the pathophysiology of AML [3-8]. Abnormal interactions between leukemic cells and the surrounding stromal cells can further enhance leukemic cell survival and proliferation [3-8]. The clinical presentation of AML can vary widely among individuals. Common symptoms include fatigue, shortness of breath, easy bruising or bleeding, recurrent infections, and bone pain. These symptoms arise due to the replacement of normal hematopoietic cells with leukemic cells in the bone marrow [2, 9-12]. AML must be accurately diagnosed using a combination of laboratory testing, clinical assessment, and bone marrow examination. Abnormal cell counts, such as elevated white blood cells, lowered platelets, and anemia, can be found with blood tests. To pinpoint certain genetic alterations, flow cytometry and cytogenetic analysis are crucial diagnostic tools [2, 9-14]. Induction chemotherapy is the primary treatment modality for AML. It aims to achieve complete remission by eliminating leukemic cells from the bone marrow [15-17]. Consolidation therapy follows induction chemotherapy to prevent disease recurrence [15-17]. Moreover, targeted therapies specifically, inhibit the function of mutated genes or proteins involved in leukemic cell growth; such as FLT3 and IDH inhibitors. These agents offer promising results in treating specific subtypes of AML [15-17]. Allogeneic stem cell transplantation is another potentially curative treatment option for eligible patients. It involves replacing the patient's diseased bone marrow with healthy stem cells from a compatible donor [15- 18]. Mesenchymal stem cells (MSCs) are multipotent cells found in various tissues, including bone marrow [18, 19]. In recent years, there has been growing interest in exploring the potential of MSCs in the treatment of AML. Myelogenous leukemia can be both actively and passively regulated by MSCs through exosome communication, cytokine-receptor interaction, and cell-to-cell contact [19]. Currently, leukemia treatment measures are not always sufficient to cure the disease because of chemo-resistance and recurrence [19]. It is evident that the targeted leukemic MSCs synergistic chemotherapeutic drug can be used more successfully and prevents drug resistance and recurrence because of the significant difference between leukemic MSCs and normal MSCs [20]. Regardless of the subtype of myeloid leukemia, MSCs provide Leukemic stem cells with malignant hematopoietic support [20]. Furthermore, the bone marrow microenvironments of leukemia and hematopoietic patients are extremely complex structures. As MSCs provide a protective microenvironment for leukemic cells to thrive and resist treatment, they play a crucial role in the maintenance and expansion of leukemic stem cells, as they secrete various cytokines and growth factors that promote leukemic cell survival and proliferation [19, 21]. On the other hand, MSCs have anti-tumorigenic properties by inhibiting the growth of tumor cells in hematological malignancies, particularly acute myeloid leukemia [22]. Some studies suggest that AML-derived MSCs can induce chemoresistance and epithelial-mesenchymal transition-like program in AML through IL-6/JAK2/STAT3 signaling pathway [23]. Moreover, Wnt signaling pathways are essential for maintaining the ability of leukemia stem cells to self-renew and for controlling the elements inside the leukemia microenvironment [24, 25]. Therefore, MSCs are a two-edged sword, and more research is still required to fully comprehend the intricate relationships and fully understand the mechanisms involved to develop effective therapeutic concepts. The potential of MSCs in the treatment of AML is an active area of research; therefore, in this paper we aim to investigate the MSCs potentials between AML patients and healthy controls. We believe that characterizing AML-MSCs compared to healthy-MSCs will help us understand their implication in the pathogenesis of AML for better therapeutic strategies.

Methods

Sample collection, isolation, and culture

In this study, 16 participants were enlisted to provide MSCs. Six were AML patients, labeled S#, and ten were healthy controls, labeled CS#. Participants signed an informed consent. Immediately following the bone marrow sample collection, density gradient centrifugation techniques using Ficoll-Paque Plus (Amersham Biosciences) were utilized to identify and purify MSCs. Reconstituted MSCs were cultivated in 25 cm^2 flasks at 37°C in 5% CO_2 after being re-suspended in Dulbecco's modified Eagle's medium (DMEM, GIBCO, USA) supplemented with 20% fetal bovine serum (FBS, GIBCO, USA) and 1% pen-strep (GIBCO, USA). This stage is noted as passage 0. The non-adherent cells were discarded at the time of media change, which is performed every three days. After the cultures achieved 80-90% confluence, cells were then passaged 1:2 approximately once per week using 0.05% Trypsin-EDTA for 5 minutes in incubator. Trypsin was deactivated with complete medium and double the volume of trypsin (GIBCO, USA). Cells were

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resuspended in 10% FBS-DMEM and left in incubator at 37°C and 5% CO_2.

All experiments were performed on MSCs from passage 2 up to passage 8 to insure consistency in results.

Characterizing the Isolated Cells

2.2.1: Colony forming unit (CFU) assay: Cells were harvested with trypsin-EDTA and centrifuged at 300 to 350 G for 10 min. Supernatant was removed, then pellet resuspend in 1 ml complete medium and cell count was performed using trypan blue. Cells were seeded at 100 cells/well in three wells of a 6 well plate in 10% FBS-DMEM. Cells were left in incubator for 14 days with medium change every 2 days.

Media was removed from the wells, washed twice with D-PBS (GIBCO, USA), and then fixed with 4% PFA for 30 minutes at room temperature. Wells were washed twice with D-PBS. Colonies were stained with 1 mL of a 0.5% crystal violet solution made with D-PBS for 15 minutes at room temperature. The wells were rinsed three times with D-PBS followed by one time with tap water. The plates were inverted on absorbent bench paper and left to air dry. The stained colonies were counted with light inverted microscope to determine the number of colonies that had more than 50 cells.

2.2.2: Flow cytometry analysis: Cells were aliquoted to 10^5 in 15 ml tubes, washed with PBS, centrifuged at 350 G for 5 minutes, and then resuspended in 100 µl D-PBS. Human Fc Binding Inhibitor Purified (20 µl) (ThermoFisher, 14-9161-73) were added and left on ice for 20 min. Then, 5 µl of the appropriate conjugated antibody or the corresponding isotype were added and incubated for 30 minutes on ice in the dark. Excess antibody were removed by washing the cells with 2 mL of Staining Buffer (ThermoFisher, 00-4222-26), then cells were centrifuged at 350 G for 5 minutes, the supernatant removed, and the cell pellet resuspended in 500 µL of Staining Buffer for flow cytometric analysis. Table 1 shows the list of the conjugated antibodies and the corresponding isotypes control used for the MSCs characterisation.

2.2.3: Cell proliferation (XTT) assay: MSCs were seeded in 96-well plates at a density of 5000 cells per well in 4 wells. Blank wells (4 wells) contained medium only (10% FBS-DMEM) to be used for background subtraction. After culturing for 3 days, 50 ul of XTT detection solution (Cell signaling, 9095S) was added to each well, returned to the incubator for three hours. Absorbance was read at 450 nm using a plate reader (Synergy HT, BioTek).

2.2.4: Apoptosis assay (Annexin-V-FITC): Cells were examined for apoptosis marker with the Annexin-V expression. Briefly, 10^5 cells were collected by centrifugation at 350 G for 5 minutes, resuspend in 96 µl of 1X Annexin V-Binding Buffer (Cell signaling, 6592S) and Incubated for 10 minutes on ice in the dark. Then 160 µl of Ice cold 1X Annexin V-Binding Buffer were added to the tubes and cells were analyzed immediately using flow cytometry.

2.2.5: Immunocytochemistry: MSCs were grown on glass coverslips, fixed in cold 4% PFA for 10 minutes, washed once with PBS, then permeabilized with 0.05% Triton X-100 in PBS for 5 minutes, and blocked with 3% BSA in D-PBS for 1 hour at room temperature. Cells were then incubated with the primary antibody at a dilution of 1:50 (ThermoFisher, 39-8401) room temperature for 1 hour, washed 3X with D-PBS, and the secondary antibody Alexa fluor 488 Donkey anti-mouse IgG (H+L) (Thermofisher, A32766) was added for 1 hour in the dark. Finally, the secondary antibody was washed 3X with D-PBS, prolong Gold anti-fade reagent with DAPI (Molecular Probes, P36935) was added, and then analyzed with a confocal microscope (Zeiss LSM 880 Airyscan).

2.2.6: Osteogenic and adipogenic differentiation: For osteogenic differentiation, cells were seeded in 6-well plates at a density of 5×10^4 cells /well in 10% FBS-DMEM. At 70% confluence, the medium was changed to osteogenic differentiation medium (StemPro Osteogenesis medium, Gibco, A10072-01). Three wells remained in 10% FBS-DMEM to be used as a negative control. Medium was changed every 3 or 4 days for 21 days. Then, the medium was discarded, and cells washed with D-PBS, and fixed with 4% PFA for 30 minutes. Finally, cells were rinsed 2x with distilled water, stained with 2% alizarin red S for 5 minutes, rinsed 3x with distilled water, and visualized under a light microscope (Zeiss stereo discovery v8). For quantification, we added 1 ml of 10% Cetylpyridinium Chloride in 10mM Sodium Phosphate, shacked the plates for 30 minutes, loaded 200 µl of each sample in 96 well plate, and plate was read at λ=570 nm.

For adipogenic differentiation, MSCs were plated as described above, the medium was changed to adipogenic differentiation medium (StemPro Adipogenesis, Gibco, A10070-01), Three wells remained in 10% FBS-DMEM for the negative control. Medium was changed every 3 or 4 days for 14 days. Then, the medium was removed, and cells washed 1x with D-PBS, and fixed with 4% PFA for 30 minutes. After fixation, cells were gently rinsed 1x with distilled water, 60% Isopropanol were added for 5 minutes, then aspirated. Oil Red O working solution was added for 5-10 minutes at room temperature. The dish was slowly rotated to spread oil red o evenly over the cells. Stain was removed, rinsed 1x with D-PBS, then hematoxylin stain was added for 1 minute at room temperature. Finally, wells were rinsed 1x with tap water and visualized under a light microscope (Zeiss stereo discovery v8). For Oil Red O quantification, cells were incubated with 250 µl of 100% isopropanol for 5-10 minutes, 200 µl of each sample were loaded into 96 well plate, and plate was read at λ=492 nm.

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Statistical analysis

Data was analyzed using statistical using t-TEST, two ways ANOVA. Results are presented as the mean ± SEM with a p-value (**p ≤ 0.01 and *p ≤ 0.05) considered statistically significant.

Results

Mesenchymal stem cells markers characterization

The expression of mesenchymal stem cells specific cell surface markers (CD105, CD90 and CD146) was consistently high in both AML-MSCs and CS-MSCs, while negative for CD45 (Figure 1A, 1B) using flow cytometry. Also, both AML-MSCs and CS-MSCs expressed the intracellular MSCs marker STRO1 (figure 2). These results confirm that the isolated population of cells are mesenchymal stem cells. These results confirm that the isolated population of cells are mesenchymal stem cells.

MSCs and apoptosis

Using flowcytometry, we used annexin v to test for apoptosis. Using the average of 3 readings per sample, our data showed that there was significantly less apoptosis in the AML-MSCs compared to the CS-MSCs for both early and late apoptosis (Figure 3A, 3B). In early apoptosis, 7.85% of CS-MSCs have undergone apoptosis, meanwhile for AML-MSCs it was only 1.15%, marking a 6.7% difference between both samples. In late apoptosis, the difference was similar with 6.13% between CS-MSCs (10.2%) and AML-MSCs (4.075%).

MSCs and proliferation

To test for proliferation, XTT assay was used. The data showed that AML-MSCs has higher proliferation when compared to CS-MSCs (Figure 4). By calculating the average of 4 readings per sample, the AML-MSCs absorbance level was reading 0.48 nm higher than CS-MSCs. In other words,

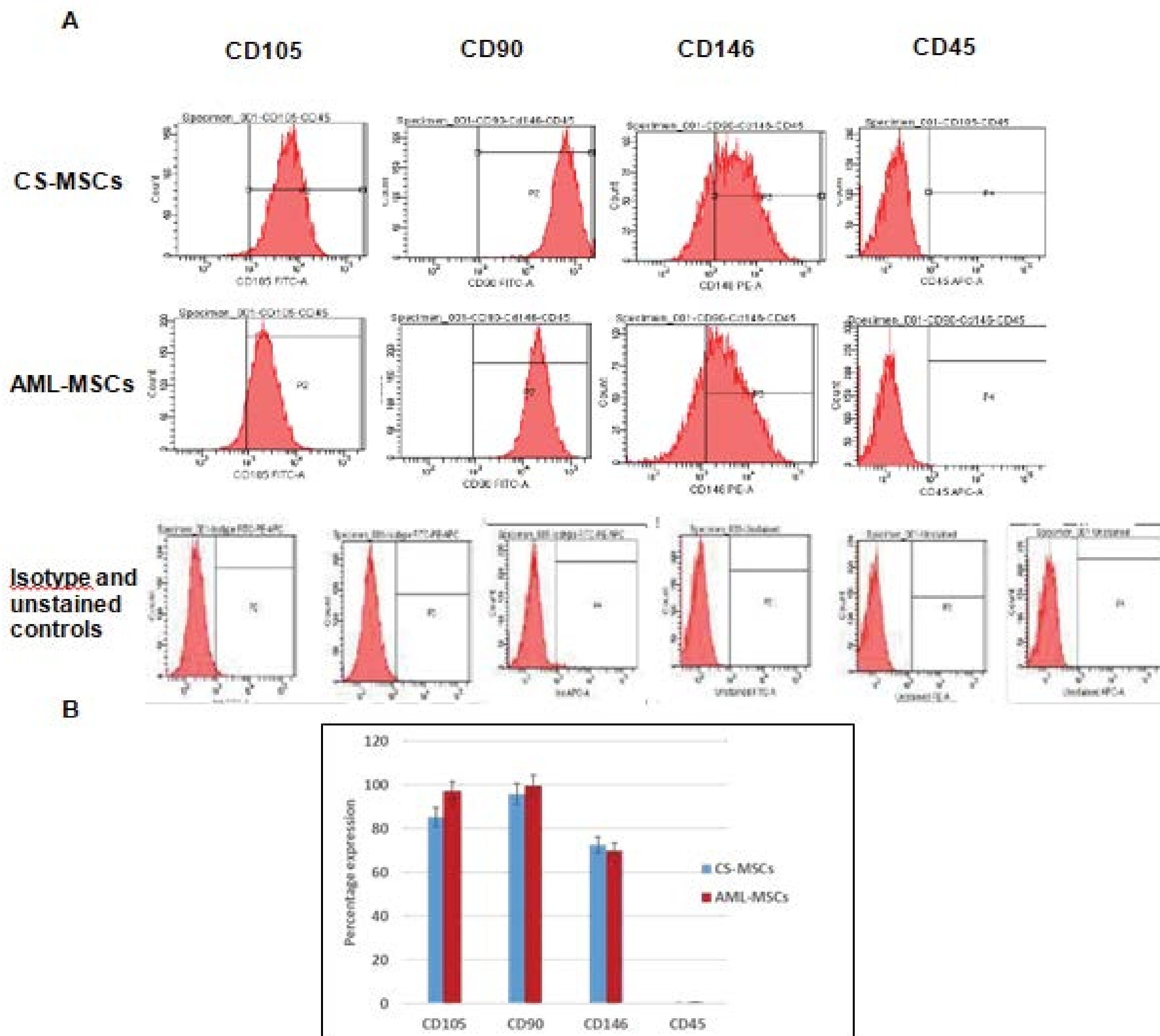

Figure 1: Expression of MSCs markers by FACS. (A) Expression of CD105, CD90, CD146 and CD45 in Control samples (CS) and acute myeloid samples (AML) MSCs. **(B)** Quantification of the expression CD105, CD90, CD146, and CD45.

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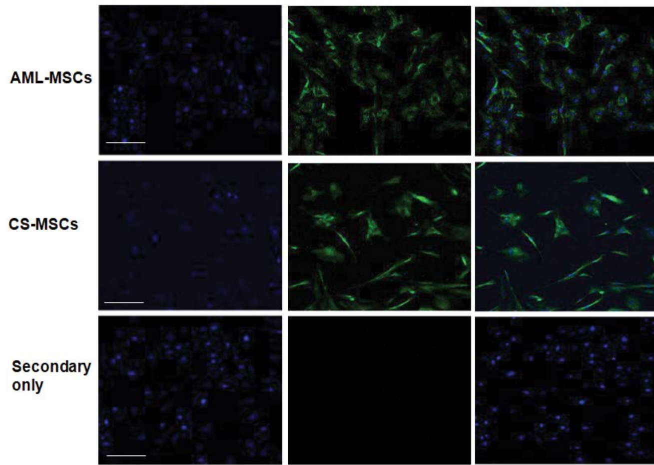

Figure 2: Immunocytochemistry for the expression of STRO1 in AML and CS of MSCs. The secondary only was used as negative control. Scale 100 µm

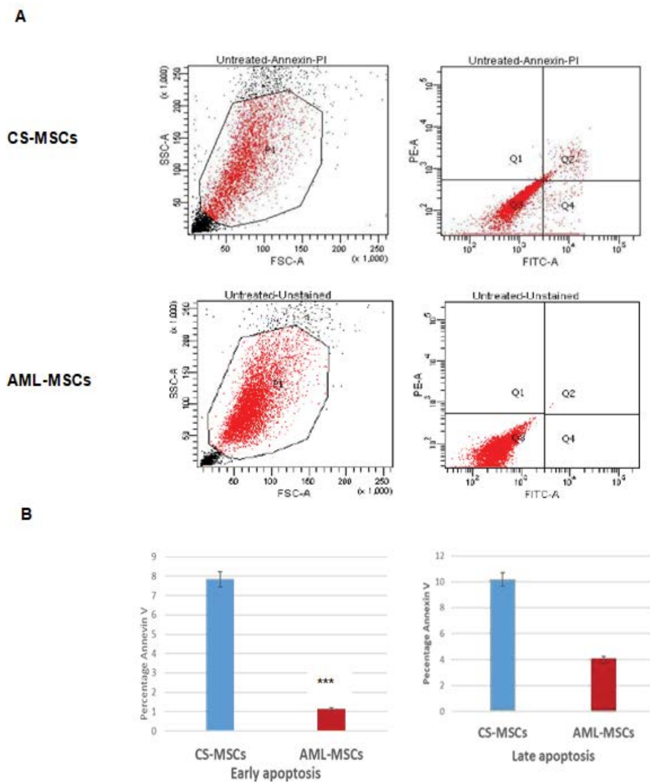

Figure 3: Apoptosis expression. (A) Representative of the control sample and the AML FACS expression for the annexin v. **(B)** Quantification of the early and late apoptosis in the AML and CS of MSCs.

AML-MSCs has higher proliferation when compared to CS-MSCs valued at 1.61 nm and 1.13 nm respectively (Figure 4). This is possibly due to the pro-tumorigenic effects displayed by MSCs in leukemic individuals, further highlighting the importance of better understanding the dual-role of MSCs in hematologic cancers.

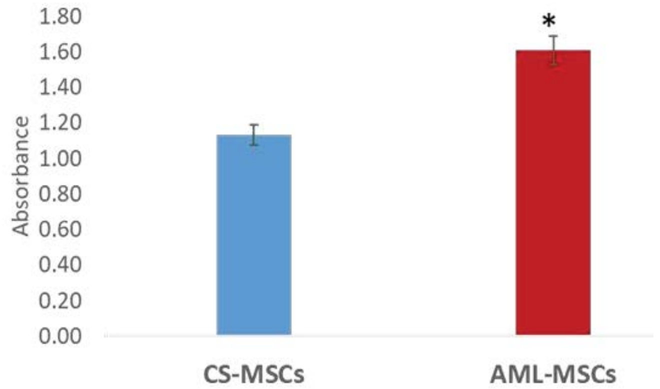

Figure 4: Cell proliferation examined using XTT assay. The AML-MSCs showed higher proliferation compared to the control samples. The graph represents the cell proliferation for all AML and CS combined together. *=$p<0.05$

Colony Forming Unit (CFU)

is a widely used test to count the number of stem cells within a population and determine the stem cells' potential for proliferation. Our results revealed that the CFU efficiency was higher in the MSCs from the AML samples compared to the control by 7.4% (Figure 5). Using the average of 4 readings per sample, AML-MSCs have 18.15% CFU efficiency compared to CS-MSCs which have 10.75% CFU efficiency.

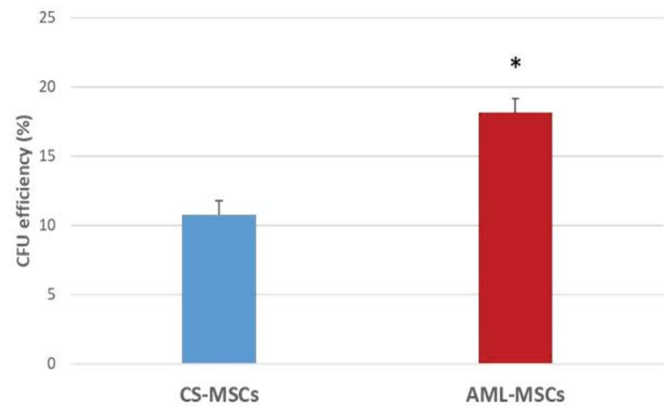

Figure 5: Graph represents the colony forming unit efficiency in the MCS from control samples and AML samples. The graph is the representation of all control samples and AML samples together.

Differentiation potential

To evaluate and compare the ability of MSCs from AML patients and control samples to differentiate into osteogenic and adipogenic lineages. Our data showed that AML-MSCs patients had higher osteogenesis compared to the CS-MSCs (Figure 6A, 6C), while there were no significant differences with the adipogenic differentiation between AML-MSCs and the control (Figure 6B, 6C).

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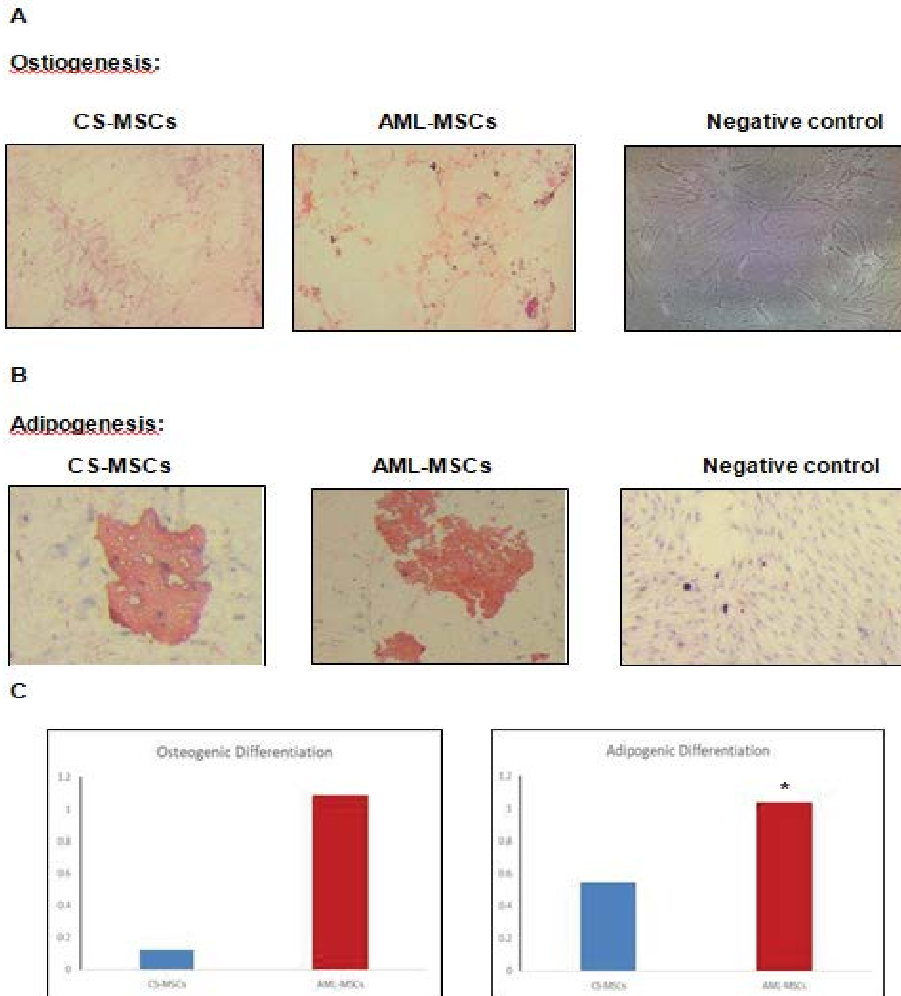

Figure 6: Cell differentiation potential. (A) Osteogenic differentiation using Alizarin Red. **(B)** Adipogenic differentiation with Oil Red O. **(C)** Quantification of the ostegenic and adipogenic differentiation.

Discussion

In our study, we showed that the MSCs isolated from either AML patients or healthy controls express MSCs specific cell surface markers (CD105, CD90 and CD146) with consistently high expression and negative for CD45. Also, the expression of the intracellular multi-potent MSCs marker STRO1 was shown to be high. These results are consistent with the successful characterization of MSCs, confirming their multi-potent nature and identity. Moreover, our data showed that the isolated MSCs heterogeneously expressed the surface marker CD146 in the AML patients and the healthy controls. $CD146^+$ cells are a subtype of MSCs mostly located in the human vascular niche. They represent 3% of the mononuclear cells inside the bone marrow [26]. The $CD146^+$ cells express Angiopoietin-1 (Ang-1) and chemokine ligand 12 (CXCL12) and interact with hematopietic stem cells (HSCs) and endothelial cells by their expression of Tie-2 and CXCR4 [26]. There is some evidence to suggest that $CD146^+$ MSCs may have a role in AML. A study comparing normal donor and AML-derived MSCs found that AML-MSCs had increased adipogenic differentiation, which might affect the support of leukemia cells [27]. $CD146^+$ cells play a major role in the communication between the bone marrow Hematopoietic Stem Cells (HSPCs) and the microenvironment [28]. Moreover, a recent study in 2023, engineered tandem CD33xCD146 CAR CIK cells to target the AML niche, suggesting that $CD146^+$ cells may be involved in the AML microenvironment [29]. Overall, there is evidence that $CD146^+$ MSCs may be involved in AML even if the data is inconclusive. A deeper investigation is required to completely comprehend the connection between $CD146^+$ MSCs and AML. On the other hand, our functional assays revealed that MSCs from AML patients had lower apoptosis, higher potency, higher proliferation, higher adipogenesis and higher osteogenesis compared to the healthy MSCs. This is largely due to MSCs displaying pro-tumorigenic and

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anti-tumorigenic effects since the predominant hypothesis regarding MSCs in leukemic individuals is that it suppresses both proliferation and apoptosis, making it a “double-edged sword” in hematologic malignancies [22]. The mechanism underlying both the pro and anti-tumorigenic properties is still poorly understood, however, the proposed and widely accepted mechanism regarding MSCs’ anti-tumorigenic effects are the induction of a cell cycle arrest. It has been reported that upon co-culturing AML cells with human bone marrow MSC stromal cell lines, it was shown that a higher percentage of AML cells were in the G1 phase and a higher percentage of AML cells in S phase without the co-culture, suggesting a possible therapeutic role of MSCs in AML [22,30]. Therefore, these data indicate that AML-MSCs could induce or maintain blast formation, decrease apoptosis to give AML-blast tolerance to treatment, increase osteogenesis to induce a hostile and supportive bone marrow niche for leukemic cells progression [31-33]. These findings might be consistent with the literature, as it is known that MSCs play a critical role in the preservation, expansion, survival, and proliferation of leukemic stem cells; thereby creating a protective milieu that allows leukemic cells to thrive and resist treatment [19-23]. In conclusion, acute myeloid leukemia remains a challenging disease to treat, often associated with poor outcomes and Mesenchymal stem cells have emerged as a potential therapeutic tool in the management of AML. MSCs unique properties, including their ability to create a protective environment for leukemic cells and their immunomodulatory effects, makes them attractive candidates for further research and clinical trials. While significant progress has been made in understanding the role of MSCs in AML, more studies are needed to fully exploit their potential and develop effective MSC-based therapies for AML patients. The heterogeneous expression of CD146 and its implications for AML pathophysiology, along with the functional disparities observed between healthy MSCs and AML-MSCs, underscores the complexity of how MSCs interact with the AML microenvironment and highlights the necessity of further exploring this field.

Data Availability

The data used to support the study's findings are included in the article.

Ethical approval

This study was approved by the Institutional Review Board of King Abdullah International Medical Research Center (KAIMRC) (Protocol# RJ15/041/J). Written informed consent was obtained from the study subjects

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Author contributions

DA and SZ contributed in all experiments and validation assays and writing the manuscript. S Alwafi, D Alsharif, and NB have contributed in cell culture work and experiments. AZ and FD helped in cell culture and manuscript revision. HA helped in collecting samples, RS helped in manuscript revision. IH and OM identified and contacted the donors to provide samples. SA contributed through the conception of the idea, the design of the work, performing experiments, and revision of the document.

Conflict of Interest

The authors declare that there is no conflict of interest.

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