# Leukemic Extracellular Vesicles as Drivers of a Pro-Inflammatory Niche

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**Abstract.** Acute myeloid leukemia (AML) cells often display resistance to conventional chemotherapy, partly due to the influence of AML-derived extracellular vesicles (AML-EVs). These vesicles, including microvesicles (MVs) and exosomes (Exos), play key roles in leukemic progression and bone marrow (BM) niche remodeling. This study investigates the effects of AML-EVs and their distinct subfractions on bone marrow–derived mesenchymal stromal cells (MSCs) and their associated functional properties. MSCs were primed with AML-EVs, AML-MVs, and AML-Exos isolated from the secretome of C1498 leukemic cells. Transcriptomic profiling revealed that AML-EVs, AML-MVs, and AML-Exos induced a pronounced pro-inflammatory transcriptional signature in MSCs. Furthermore, AML-EVs and their subfractions skewed MSCs differentiation toward the adipogenic lineage, suppressing osteogenic differentiation. Overall, this study identifies a previously unrecognized role of AML-EVs, including their fractions, viz. MVs and Exos, in reprogramming the BM niche which offer new insights into the mechanisms driving AML progression and chemoresistance. This would pave the way for developing novel niche-targeted therapies to combat AML.

**Keywords:** Acute Myeloid Leukemia, Extracellular vesicles, Microvesicles, Exosomes, Mesenchymal stromal cells.

## 1 Introduction

Acute Myeloid Leukemia (AML) is a predominant hematologic malignancy in adults, characterized by the uncontrolled clonal expansion of aberrant hematopoietic progenitors that infiltrate the bone marrow (BM) and peripheral blood, culminating in the disruption of normal hematopoiesis (1). Tumor-associated inflammation disrupts the equilibrium of the hematopoietic niche, perturbing the function of both hematopoietic stem and progenitor cells (HSPCs) and mature immune populations within the BM niche (2). Cytokine network dysregulation further exacerbates this process by establishing a pro-tumorigenic microenvironment that promotes leukemic cell proliferation, survival, and chemoresistance (3,4). Due to a pro-inflammatory


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cytokine exposure, dysregulation of immune cell states is a hallmark of hematological disease and neoplasia (5). Although the immune microenvironment critically regulates the initiation, progression, and therapeutic response of hematological malignancies (HM), the precise mechanisms by which leukemic cytokines modulate immune cell function to either facilitate or constrain leukemia remain poorly understood. Moreover, the role of AML-derived extracellular vesicles (AML-EVs) in driving inflammation during HM has yet to be fully elucidated.

Our study establishes a groundwork of AML-EVs and their fractions, viz. AML-derived microvesicles (AML-MVs) and AML-derived exosomes (AML-Exos) in promoting leukemic–stromal communication within the BM niche. This study delineates the transcriptional changes induced by AML-EVs and their subfractions, inducing inflammation, promoting adipogenesis and suppressing osteogenesis in MSCs. However, the mechanisms behind the BM niche remodeling by AML-EVs and their fractions supporting inflammation remain unclear. This study would pave the way for developing niche-targeted therapies in AML

## 2 Materials and methods

### 2.1 Material

#### 2.1.1 Animals

All experimental protocols have been approved by the Institutional Animal Ethics Committee (IAEC) of the Symbiosis School of Biological Sciences (SSBS) (Approval Number: IAEC/SSBS/01-2024). C57BL/6J mice were obtained from the Advanced Centre for Treatment Research, and Education in Cancer (ACTREC), Mumbai. Mice were housed and bred in the SSBS experimental animal facility. 6-8 weeks old mice were used for all experiments.

#### 2.1.2. Other Reagents Used

Iscove's Modified Dulbecco's Medium (IMDM) (HiMedia, Mumbai, India), Fetal Bovine Serum (Gibco, Thermo Fisher Scientific, New York, USA), Glutamine, Penicillin, Streptomycin (HiMedia, Mumbai, India), Power up SYBR green polymerase chain reaction (PCR) master mix (Applied Biosystems, Invitrogen, USA), Trizol (Sigma, USA), PrimeScriptTM RT reagent kit (Perfect Real Time), (Takara, Shiga, Japan), Chloroform (Sigma, USA), Trypan blue dye (HiMedia, Mumbai, India), Pierce BCA Protein Assay Kit (Thermo Scientific™, USA), Trehalose (Sigma, USA), Alazarin Red (Sigma, USA), Oil red O (Sigma, USA), Safranin O (Sigma, USA), Cetylpyridine (HiMedia, Mumbai, India), Paraformaldehyde (Sigma, USA). Stempro Adipocyte and Osteogenic differentiation Basal medium and supplement (Gibco, USA).

## 2.2 Methodology:

### 2.2.1. Cell lines

C1498, a lymphoblastic cell line isolated from a female mouse with acute myeloid leukemia, was procured from the American Type Culture Collection (TIB-49, ATCC). Cells were cultured in Iscove's Modified Dulbecco's Medium (IMDM) supplemented with 10% fetal bovine serum (FBS) and incubated at 37□C/5% CO2.

### 2.2.2. Isolation and protein estimation of EVs, MVs, and Exos

C1498 cells were cultured in the growth medium for 48 hours. The cells were washed, and then 1.2 × 10^6 cells were then seeded in DMEM supplemented with 10% EV-depleted FBS and cultured for another 48 hours, after which the cell suspension was collected and subjected to centrifugation at 2600g for 10 min to remove cell debris. The supernatant was termed "Conditioned Medium (CM)". The CM was further utilized for ultracentrifugation as described previously (6) to isolate EVs, MVs, and Exos. For protein extraction, a 15 µL aliquot of each sample of EVs, MVs and Exos was incubated with 4× RIPA lysis buffer for 1 hour on ice, with intermittent vortexing every 10 minutes. Protein concentration was quantified using the Bicinchoninic Acid (BCA) protein assay kit (as per the vendor's instructions.

### 2.2.3. Isolation and priming of MSCs

C57BL/6J mice (6-8 weeks old) were euthanized by CO2 asphyxiation, and total BM cells were harvested from the femurs and tibiae and suspended in IMDM supplemented with 10% FBS. Non-adherent cells were removed, and adherent cells were subsequently cultured. For all experiments, MSCs were subcultured till passage 3 and were exposed to AML-EVs, AML-MVs, and AML-Exos for 48 hours and were termed as "primed MSCs". The MSCs not exposed to AML-EVs or their fractions were termed as "unprimed MSCs".

### 2.2.4. RNA isolation and qRT-PCR

TRIzol method was used to extract RNA from unprimed and primed MSCs. The RNA was quantified using a Synergy H1 microplate reader (BioTek, USA). The cDNA was then synthesized using the PrimeScriptTM RT reagent kit (Perfect Real Time), and quantitative RT-PCR (qRT-PCR) was performed using CFX opus 96 Real Time PCR (Biorad, USA) using the specific primers (Supp. Table 1) and SYBR green master mix, as described previously (7). Gene expression was normalized using GAPDH expression. Relative gene expression was calculated as RQ = 2^-ΔΔCt.

### 2.2.5. Differentiation of MSCs into adipogenic and osteogenic lineages

MSCs were seeded at a density of $2 \times 10^4$ cells/well in IMDM supplemented with 10% FBS. Cells were incubated under standard culture conditions for 24 hours to allow cell attachment. Post incubation, MSCs were primed for 48 hours with AML-EVs, AML-MVs, and AML-Exos. Following priming, the culture medium was replaced with a 1:1 mixture of lineage-specific differentiation medium and IMDM, supplemented with 10% FBS, to induce adipogenic and osteogenic differentiation. The media was changed

every 72 hours for 21 days. After 21 days, the cells were fixed with 4% paraformaldehyde (PFA) for 15 minutes at room temperature (RT), followed by washing with distilled water ($dH_2O$). Subsequently, lineage-specific staining was performed using Oil Red O for adipogenic differentiation and Alizarin Red S for osteogenic differentiation. Staining was carried out for 20 minutes at RT, followed by washing with $dH_2O$ twice. Stained cells were imaged using a phase-contrast microscope (Carl Zeiss, Germany), and quantitative assessment of dye retention was done using a Synergy H1 microplate reader (BioTek, USA).

#### 2.2.6. Statistical Analysis

Results were analysed using a one-way ANOVA test. $p<0.05$ was considered statistically significant. Results were expressed as mean value ± SD. GraphPad Prism software (Version 8, San Diego, CA) was used for statistical analyses.

## 3 Results

### 3.1 AML-EVs affect the proliferation of MSCs:

To evaluate the effect of AML-EVs and their fractions (AML-MVs and AML-Exos) on MSCs, we primed the MSCs with increasing concentrations (2, 4, 6, and 8 µg, respectively) of AML-EVs and their fractions for 48 hours, while unprimed (UP) MSCs served as the control group. We observed that exposure of MSCs to AML-EVs, AML-MVs, or AML-Exos led to a significant reduction in the number, as compared to unprimed ones. All types of EVs produced a similar inhibitory effect on MSC growth across the tested concentrations. Moreover, there was no statistically significant difference among the various primed groups (AML-EVs, AML-MVs, and AML-Exos) at a given concentration, nor between the different concentrations tested (2, 4, 6, and 8 µg) (Fig. 1). Therefore, we selected 4 µg as the median concentration for subsequent experiments. These findings indicate that although AML-EVs, AML-MVs, and AML-Exos exert a significant inhibitory effect on MSC growth, this inhibition is independent of EV type or concentration.

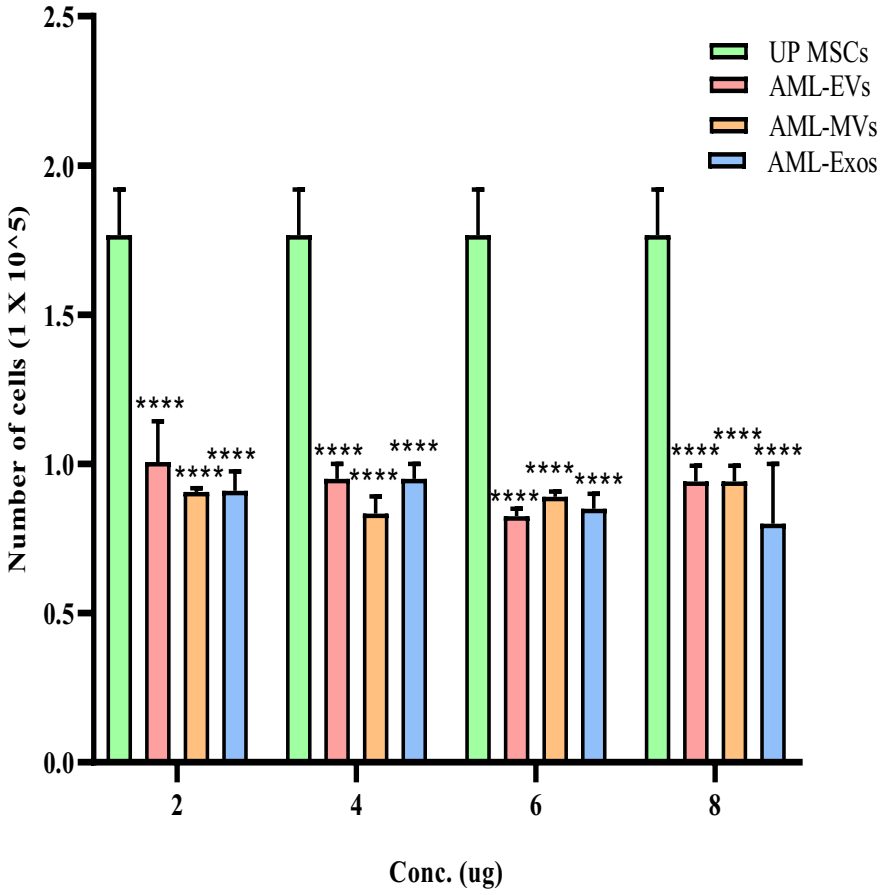


**Fig. 1. AML-EVs, AML-MVs, and AML-Exos decrease the proliferation of MSCs**:

The graph represents the standardization of AML-EVs, AML-MVs, and AML-Exos concentration for priming MSCs for 48hours. The data show a significant reduction in the proliferation of primed MSCs, as compared to the unprimed MSCs (black asterisk); however, there was no significant difference in growth pattern within the primed groups (ns). The data represent mean ± SD. *p< 0.05, ** p<0.01, ***p<0.001.

### 3.2 AML-EVs promote inflammation within the BM niche.

Inflammation is a key determinant of AML pathophysiology, orchestrating both structural and functional reprogramming of the bone marrow niche (8-12). To

determine whether AML-EVs induce pro-inflammatory markers in MSCs, we cultured MSCs with AML-EVs, MVs, and Exos (primed MSCs) for 48 hours and subsequently performed qRT-PCR analyses. The primed MSCs exhibited significantly elevated expression of inflammatory mediators, including interferon regulatory factor 7 (*Irf7*), interleukin-6 (*Il-6*), and interferon regulatory factor 3 (*Irf3*) (Fig. 2A–D). However, the magnitude of induction varied across the different EV fractions. Total EVs upregulated the expression of *Irf7*, *Il6,* and *Irf3*, and downregulated the expression of *Ifn-γ* in the primed MSCs (Fig. 2A- D, second bars). In contrast, MSCs primed with AML-MVs showed markedly higher expression of *Irf7* and *Il-6*, *Irf3* (Fig. 2A, 2B, and 2D; third bars). MSCs primed with AML-Exos displayed increased expression of all the inflammatory mediators examined (Fig. 1A–D; fourth bars), especially that of *Ifn-* (Fig. 2C, fourth bar) and also that of *Irf3* (Fig. 2D, fourth bar). Collectively, these findings demonstrate that AML-EVs elicit a robust inflammatory transcriptional response in MSCs, underscoring their role as potent mediators of inflammation-driven remodeling of the bone marrow microenvironment (BME). Moreover, our results reveal distinct contributions of AML-MVs and AML-Exos in activating specific inflammatory pathways.

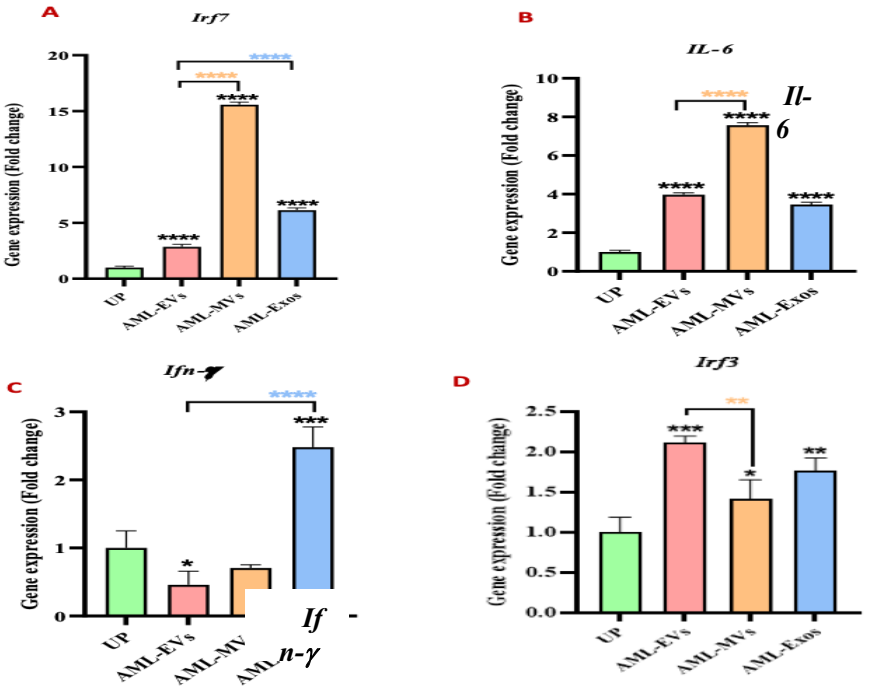


**Fig. 2. Primed MSCs show an increase in inflammatory markers (A-D)**

The graph represents qRT-PCR analysis of inflammatory markers interferon regulatory protein 7 *(Irf7)* **(A),** interleukin-6 **(***Il-6)* **(B),** interferon gamma **(***Ifn-γ)* **(C)** and interferon regulatory protein 3 (*Irf3)* **(D).** The data show that primed MSCs, particularly AML-MVs, showed an increase in *Irf7* and *Il-6* **(A & B)** (n=3), while AML-Exos showed a striking increase, and AML-EVs showed a reduction with respect to *Ifn-γ* **(C) (n-3).** The graphs depict that all the primed groups showed a remarkable increase in *Irf3* **(D) (n=3),** as compared to the unprimed group. Gene expression was normalized using using glyceraldehyde-3-phosphate dehydrogenase *(Gapdh)* expression. The data represent mean ± SD. *p< 0.05, ** p<0.01, ***p<0.001. The significance is shown in a black asterisk (***) with respect to the unprimed MSCs. However, the orange-colored asterisk (**) indicates the significance of MSCs primed with AML-MVs, and the blue-colored asterisk (**) indicates the significance of MSCs primed with AML-Exos with respect to the MSCs primed with EVs.

### 3.3 AML-EVs alter the differentiation-specific gene expression in the MSCs

Bone Marrow adipogenesis accompanied by loss of bone density is another hallmark of the leukemic niche (13-15). To assess the influence of AML-EVs and their distinct fractions, microvesicles (MVs) and exosomes (Exos), on MSC differentiation, we first analyzed the expression of lineage-specific genes associated with osteogenesis such as osteocalcin and bone morphogenetic protein 4 (*Ocn, Bmp4*) and adipogenesis, CCAAT/enhancer-binding protein alpha (*Cebp-α*) (Fig. 3A-C). We observed a significant downregulation of osteogenic markers *Ocn* and *Bmp4* in all vesicle-primed MSCs compared with unprimed controls. Specifically, *Ocn* expression was most markedly reduced in MSCs primed with AML-MVs, followed by AML-Exos (Fig. 3A, third and last bars), whereas *Bmp4* expression was suppressed across all primed groups, with the strongest inhibition observed in AML-MVs, followed by AML-Exos and AML-EVs (Fig. 3B, third, fourth and second bars). These results indicate that AML-EVs impair the osteogenic commitment of MSCs. Conversely, the adipogenic transcription factor *Cebp-α* was significantly upregulated in MSCs primed with AML-Exos (Fig. 3C, fourth bar), followed by AML-EVs (Fig. 3C, second bar), suggesting enhanced adipogenic potential upon exposure to AML-derived vesicles. These findings imply that AML-EV priming rapidly modulates MSC lineage commitment, potentially through distinct signaling cues delivered by each vesicle subtype.

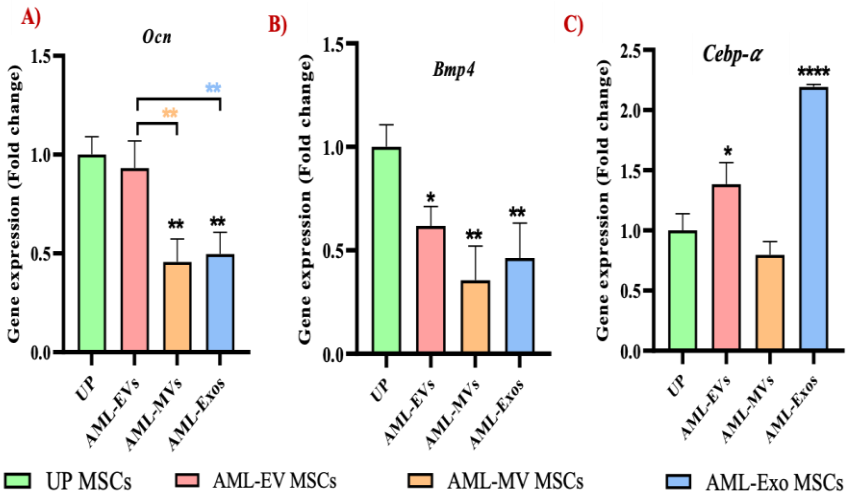


**Fig. 3. Primed MSCs show alteration in differentiation genes**

The graphs represent qRT-PCR analysis of control and primed MSCs, and show a reduction in osteogenesis genes, osteocalcin (*Ocn)* and bone morphogenic protein 4 (*Bmp4)* **(A & B) (n=3)** in the primed MSCs. The data show an increase in adipogenesis gene**,** CCAAT/enhancer-binding protein alpha (Cebp-$\alpha$) **(C),** in primed MSCs **(n=3)**. Gene expression was normalized *Gapdh* expression. The data represent mean ± SD. *p< 0.05, ** p<0.01, ***p<0.001. The significance is shown in a black asterisk (***) with respect to the unprimed MSCs. However, the orange-colored asterisk (**) indicates the significance of MSCs primed with AML-MVs, and the blue-colored asterisk (**) indicates the significance of MSCs primed with AML-Exos with respect to the MSCs primed with EVs.

### 3.4 AML-EVs Promote Marrow Adipogenesis and Suppress Osteogenesis.

To further substantiate the gene expression data with functional data, MSCs were continuously exposed to AML-EVs, AML-MVs, or AML-Exos during lineage-specific differentiation for 21 days. Oil Red O staining revealed abundant lipid droplet accumulation in all primed MSCs, compared with unprimed controls (Fig. 4A), with the most pronounced effect seen in AML-MVs and AML-Exos primed MSCs. Quantitative analysis of Oil Red O absorbance at 540 nm confirmed this trend (Fig. 4B), indicating that AML-EVs, particularly Exos, promote adipogenic differentiation of MSCs. In contrast, Alizarin Red staining revealed a marked reduction in calcium deposition in all AML-EV-primed MSCs relative to controls (Fig. 4C). Quantitative analysis confirmed that osteogenic differentiation was most strongly suppressed in

MSCs primed with AML-MVs, followed by AML-Exos, while total AML-EVs exerted a comparatively moderate inhibitory effect (Fig.4D, third and fourth bars).

Collectively, these findings demonstrate that AML-derived EVs distinctly reprogram MSC fate, promoting adipogenic differentiation while suppressing osteogenesis, thereby contributing to the lineage skewing characteristic of the leukemic bone marrow microenvironment.

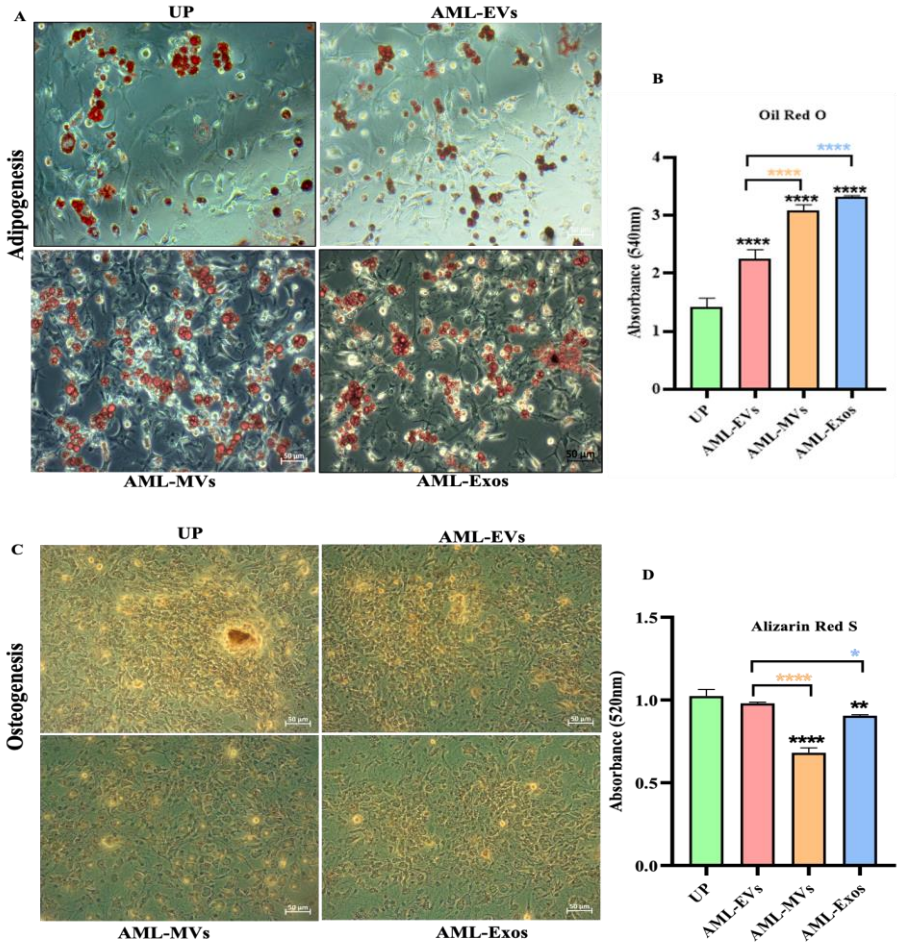


**Fig. 4. Oil Red O, and Alizarin Red S staining and quantification of absorbance showed alteration in differentiation properties of primed MSCs**

Phase contrast images of unprimed, AML-EVs, AML-MVs and AML-Exos primed MSCs showed enhanced adipogenesis **(A).** The quantification of absorbance also

corroborated the same **(B)**. The phase contrast images of unprimed and AML-EVs, AML-MVs and AML-Exos primed MSCs showed decrease in osteogenesis **(C)** and quantification of the absorbance also corroborated the same **(D) (n=3)**. The data represent mean ± SD. *p< 0.05, ** p<0.01, ***p<0.001. The significance is shown in a black asterisk (***) with respect to the unprimed MSCs. However, the orange-colored asterisk (**) indicates the significance of MSCs primed with AML-MVs, and the blue-colored asterisk (**) indicates the significance of MSCs primed with AML-Exos with respect to the MSCs primed with EVs.

## 4 Discussion

Our study shows that AML-derived EVs and their fractions viz. AML-MVs and AML-Exos reprogram the BM niche specifically MSCs in such a way that MSCs secrete pro-inflammatory cytokines and compromise their differentiation capability. The MSCs were more biased towards adipogenesis, and osteogenesis was observed to be reduced in the primed MSCs as compared to the unprimed MSCs. These results suggest that AML-EVs transform the normal BM niche into an inflammatory BM niche, perturbing normal hematopoiesis and promoting leukemogenesis. However, we would also like to corroborate this phenomenon by using non-AML lymphocyte-derived EVs to see whether the observed effect is specific to AML-EVs and their fractions.

## 5 Conclusion

Overall, our study highlights that the AML-derived EVs and their fractions, i.e., MVs and Exos, secrete pro-inflammatory markers in the BM niche and alter the differentiation capabilities of the MSCs. This remodeling of the BM niche would impair normal haematopoiesis and support leukemogenesis leading to the AML progression.

**Ethics Declaration:** All experimental protocols have been approved by the Institutional Animal Ethics Committee (IAEC) of the Symbiosis School of Biological Sciences (SSBS) (Approval Number: IAEC/SSBS/01-2024).

**Conflict of Interest:** The authors declare that they have no conflict of interest.

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**Clinical Trials:** Not applicable.

**Data Availability Statement**: Data will be available upon reasonable request.

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