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Ingrid L. M. Souza1, *, Andreia A. Suzukawa1, Raphaella Josino2, Bruna H. Marco1,3, Anny W. Robert1,3, Patrícia Shigunov1, Alejandro Correa1,* and Marco A. Stimamiglio1,*

1Laboratory of Basic Biology of Stem Cells (Labcet), Carlos Chagas Institute, Fiocruz, Curitiba 81350-010, PR, Brazil
2Albert Einstein Israelite Hospital, São Paulo 05652-900, SP, Brazil
3Confocal and Electronic Microscopy Facility (RPT07C), Carlos Chagas Institute, Fiocruz, Curitiba 81350-010, PR, Brazil

Responses of Skin Cells, Endothelial Cells and Macrophages Induced by Human Mesenchymal Stem/Stromal Cell-Derived Extracellular Vesicles Isolated from Microcarrier Culture

Abstract: Mesenchymal stem/stromal cells (MSCs) and their extracellular vesicles (MSC-EVs) have been described to have importantroles in tissue regeneration, includingtissue repair, controlof inflammation, enhancing angiogenesis, and regulating extracellular matrix remodeling. MSC-EVs are suitable for use in regeneration therapies regarding some of their features such as facility for dosage,histocompatibility, and low immunogenicity, thus possessing a lower possibility of rejection. In this work, we address the potential activity of MSC-EVs isolated from adipose-derived MSCs (ADMSC-EVs) cultured on cross-linked dextran microcarriers, applied to test the scalability and reproducibility of EV production. Human dermal fibroblasts (NHDF-1), keratinocytes (HaCat), endothelial cells (HUVEC), and THP-1 cell-derived macrophages were treatedin vitro with ADMSC-EVs in order to have their cellular responsesevaluated (i.e., cell proliferation, cell migration, angiogenesis induction, and macrophage phenotype-switching). ADMSC viability and phenotypewere assessed during cell cultureand isolated ADMSC-EVswere analyzed by nanotracking particle analysis, electron microscopy, and immunophenotyping. We observed an enhancement of HaCat proliferation; NHDF-1 and HaCat migration; endothelial tube formation on HUVEC; and the expression of inflammatory cytokinesin THP-1-derived macrophages. The increased expression of TGF-β and IL-1β was observed in M1 macrophages treated with higher concentrations of ADMSC-EVs. Hence, EVs from microcarrier-cultivated ADMSCs are shown to modulatecell behavior, being able to induce skin cells to migrate and proliferate as well as stimulate angiogenesis and cause balancebetween pro- and anti-inflammatory responsesin macrophages. Based on these findings, we suggest that the isolation of EVs from microcarrier- cultured ADMSCs makes it possible to induce in vitro cellular responses of interest and obtain scalable particle numbers for the development of in vivo concept tests for tissue regeneration studies.

Keywords: extracellular vesicles; ADMSCs; wound repair;angiogenesis; macrophage polarization.

Biography: Ingrid Larissa Melo de Souza, Carlos Chagas Institute (ICC) Fiocruz-Paraná, Brazil Postdoctoral researcher in Cellular Biology at Carlos Chagas Institute- FIOCRUZ in Curitiba, Brazil phD and Msc in Cellular and Molecular Biology by the Federal University of Paraná (UFPR) in Curitiba, Brazil Bachelor in Biology by the Federal University of Santa Catarina (UFSC) in Florianópolis, Brazil

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