ML 21-17 (31/08/2021)

Pharmaceutics
-
-
-
. 2021 Jul 23;13(8):1129.
doi: 10.3390/pharmaceutics13081129.

Freeze-Dried Mesenchymal Stem Cell-Secretome Pharmaceuticalization: Optimization of Formulation and Manufacturing Process Robustness

Michela Mocchi[1], Elia Bari[1], Giorgio Marrubini[1], Andrea Foglio Bonda[2,3], Sara Perteghella[1,4], Fulvio Tartara[5], Fabio Cofano[6,7], Giuseppe di Perna[6], Lorella Giovannelli[2], Delia Mandracchia[8], Marzio Sorlini[4,9], Diego Garbossa[6], Maria Luisa Torre[1,4], Lorena Segale[2,3]
Affiliations expand

- PMID: 34452088

- PMCID: PMC8401234

- DOI: 10.3390/pharmaceutics13081129

Abstract

Producing mesenchymal stem cell (MSC)-secretome for dose escalation studies and clinical practice requires scalable and good manufacturing practice (GMP)-compliant production procedures and formulation into a standardized medicinal product. Starting from a method that combines ultrafiltration and freeze-drying to transform MSC-secretome into a pharmaceutical product, the lyosecretome, this work aims to: (i) optimize the lyosecretome formulation; (ii) investigate sources of variability that can affect the robustness of the manufacturing process; (iii) modify the ultrafiltration step to obtain a more standardized final product. Design of experiments and principal component analysis of the data were used to study the influence of batch production, lyophilization, mannitol (M)/sucrose (S) binary mixture, selected as cryoprotectant excipients, and the total amount of excipients on the extracellular vesicles (EV) particle size, the protein and lipid content and the in vitro anti-elastase. The different excipients ratios did not affect residual moisture or EV particle size; simultaneously, proteins and lipids were better preserved in the freeze-dried product

using the maximum total concentration of excipients (1.5% *w/v*) with a M:S ratio of about 60% *w/w*. The anti-elastase activity was instead better preserved using 0.5% *w/w* of M as excipient. The secretome batch showed to be the primary source of variability; therefore, the manufacturing process has been modified and then validated: the final product is now concentrated to reach a specific protein (and lipid) concentration instead of cell equivalent concentration. The new standardization approach led to a final product with more reproducible quali-quantitative composition and higher biological activity.

J Neurosurg
. 2021 Aug 27;1-11.
doi: 10.3171/2021.3.JNS203045. Online ahead of print.

Characterization of patient-derived bone marrow human mesenchymal stem cells as oncolytic virus carriers for the treatment of glioblastoma

Yuzaburo Shimizu[1,2,3], Joy Gumin[1,2], Feng Gao[1,2], Anwar Hossain[1,2], Elizabeth J Shpall[4], Akihide Kondo[3], Brittany C Parker Kerrigan[1,2], Jing Yang[1,2], Daniel Ledbetter[1,2], Juan Fueyo[5,2], Candelaria Gomez-Manzano[5,2], Frederick F Lang[1,2]
Affiliations expand

- PMID: 34450587

- DOI: 10.3171/2021.3.JNS203045

Abstract

Objective: Delta-24-RGD is an oncolytic adenovirus that is capable of replicating in and killing human glioma cells. Although intratumoral delivery of Delta-24-RGD can be effective, systemic delivery would improve its clinical application. Bone marrow-derived human mesenchymal stem cells (BM-hMSCs) obtained from healthy donors have been investigated as virus carriers. However, it is unclear whether BM-hMSCs can be derived from glioma patients previously treated with marrow-toxic chemotherapy or whether such BM-hMSCs can deliver oncolytic viruses effectively. Herein, the authors undertook a prospective clinical trial to determine the feasibility of obtaining BM-hMSCs from patients with recurrent malignant glioma who were previously exposed to marrow-toxic chemotherapy.

Methods: The authors enrolled 5 consecutive patients who had been treated with radiation therapy and chemotherapy. BM aspirates were obtained from the iliac crest and were cultured to obtain BM-hMSCs.

Results: The patient-derived BM-hMSCs (PD-BM-hMSCs) had a morphology similar to that of healthy donor-derived BM-hMSCs (HD-BM-hMSCs). Flow cytometry revealed that all 5 cell lines expressed canonical MSC surface markers. Importantly, these cultures could be made to differentiate into osteocytes, adipocytes, and chondrocytes. In all cases, the PD-BM-hMSCs homed to intracranial glioma xenografts in mice after intracarotid delivery as effectively as HD-BM-hMSCs. The PD-BM-hMSCs loaded with Delta-24-RGD (PD-BM-MSC-D24) effectively eradicated human gliomas in vitro. In in vivo studies, intravascular administration of PD-BM-MSC-D24 increased the survival of mice harboring U87MG gliomas.

Conclusions: The authors conclude that BM-hMSCs can be acquired from patients previously treated with marrow-toxic chemotherapy and that these PD-BM-hMSCs are effective carriers for oncolytic viruses.

Biomolecules
-
-
-
. 2021 Aug 2;11(8):1141.
doi: 10.3390/biom11081141.

The Role of Mesenchymal Stem Cells (MSCs) in Veterinary Medicine and Their Use in Musculoskeletal Disorders

Przemysław Prządka[1], Krzysztof Buczak[1], Ewelina Frejlich[2], Ludwika Gąsior[3], Kamil Suliga[4], Zdzisław Kiełbowicz[1]
Affiliations expand

- PMID: 34439807
- PMCID: PMC8391453
- DOI: 10.3390/biom11081141

Abstract

Regenerative medicine is a dynamically developing field of human and veterinary medicine. The animal model was most commonly used for mesenchymal stem cells (MSCs) treatment in experimental and preclinical studies with a satisfactory therapeutic effect. Year by year, the need for alternative treatments in veterinary medicine is increasing, and other applications for promising MSCs and their biological derivatives are constantly being sought. There is also an increase in demand for other methods of treating disease states, of which the classical treatment methods did not bring the desired results. Cell therapy can be a realistic option for treating human and animal diseases in the near future and therefore additional research is needed to optimize cell origins, numbers, or application methods in order to standardize the treatment process and assess its effects. The aim of the following work was to summarize available knowledge about stem cells in veterinary medicine and their possible application in the treatment of chosen musculoskeletal disorders in dogs and horses.

J Stem Cells Regen Med

. 2021 Mar 10;17(1):28-34.
doi: 10.46582/jsrm.1701004. eCollection 2021.

Osteogenic differentiation potential and quantification of fresh and cryopreserved dental follicular stem cells-an *in vitro* analysis

Maryam AlHindi[1], Manju Roby Philip[1]
Affiliations expand

- PMID: 34434005
- PMCID: PMC8372412
- DOI: 10.46582/jsrm.1701004

Free PMC article

Abstract

Purpose: To isolate and characterize mesenchymal stem cells of dental follicle from fresh and cryopreserved samples and to test any significant difference in their osteogenic differentiation potential by using digital imaging software. We also investigated whether the cryoprotectant used and its concentration is able to maintain cell count and viability. **Methods**: Mesenchymal stem cells (MSCs) were isolated from dental follicle of impacted third molars. The osteogenic differentiation potential of dental follicle stem cells was assessed using alizarin red and alkaline phosphatase staining followed by digital imaging quantification of the stains. **Results**: Dental follicle cells have shown typical characterisation by exhibiting the stem cell stromal markers and hematopoietic markers, but there was variance in the percentage of expression in fresh and cryopreserved samples. There was considerable osteogenic differentiation potential in the fresh sample compared to cryopreserved sample. The cell count and viability were preserved in both samples. **Conclusions**: The results in the study have shown wide variation of osteogenic differentiation potential in fresh and cryopreserved samples. Also, the cryoprotectant was found to be effective in its purpose at the specified concentration.

Transl Lung Cancer Res
-
-
-
. 2021 Jul;10(7):3369-3384.
doi: 10.21037/tlcr-20-1134.

A narrative review on tumor microenvironment in oligometastatic and oligoprogressive non-small cell lung cancer: a lot remains to be done

Lorenzo Belluomini[1], Alessandra Dodi[1], Alberto Caldart[1], Dzenete Kadrija[1], Marco Sposito[1], Miriam Casali[1], Giulia Sartori[1], Miriam Grazia Ferrara[2], Alice Avancini[3], Emilio Bria[2], Jessica Menis[4,5], Michele Milella[1], Sara Pilotto[1]
Affiliations expand

- PMID: 34430373
- PMCID: PMC8350097
- DOI: 10.21037/tlcr-20-1134

Free PMC article

Abstract

Objective: In this review, we aim to collect and discuss available data about the role and composition of tumor microenvironment (TME) in oligometastatic (OMD) and oligoprogressive (OPD) non-small cell lung cancer (NSCLC). Furthermore, we aim to summarize the ongoing clinical trials evaluating as exploratory objective the TME composition, through tissue and/or blood samples, in order to clarify whether TME and its components could explain, at least partially, the oligometastatic/oligoprogressive process and could unravel the existence of predictive and/or prognostic factors for local ablative therapy (LAT).

Background: OMD/OPD NSCLC represent a heterogeneous group of diseases. Several data have shown that TME plays an important role in tumor progression and therefore in treatment response. The crucial role of several types of cells and molecules such as immune cells, cytokines, integrins, protease and adhesion molecules, tumor-associated macrophages (TAMs) and mesenchymal stem cells (MSCs) has been widely established. Due to the peculiar activation of specific pathways and expression of adhesion molecules, metastatic cells seem to show a tropism for specific anatomic sites (the so-called "seed and soil" hypothesis). Based on this theory, metastases appear as a biologically driven process rather than a random release of cancer cells. Although the role and the function of TME at the time of progression in patients with NSCLC treated with tyrosine-kinase inhibitors and immune checkpoint inhibitors (ICIs) have been investigated, limited data about the role and the biological meaning of TME are available in the specific OMD/OPD setting.

Methods: Through a comprehensive PubMed and ClinicalTrials.gov search, we identified available and ongoing studies exploring the role of TME in oligometastatic/oligoprogressive NSCLC.

Conclusions: Deepening the knowledge on TME composition and function in OMD/OPD may provide innovative implications in terms of both prognosis and prediction of outcome in particular from local treatments, paving the way for future investigations of personalized approaches in both advanced and early disease settings.

Res Vet Sci

-
-
-

. 2021 Aug 13;140:117-124.
doi: 10.1016/j.rvsc.2021.08.006. Online ahead of print.

Canine dental pulp and umbilical cord-derived mesenchymal stem cells as

alternative sources for cell therapy in dogs

Paulo Henrique Utumi[1], Letícia Fracaro[2], Alexandra Cristina Senegaglia[3], Felipe Yukio Ishikawa Fragoso[2], Dayane Mayumi Miyasaki[2], Carmen Lucia Kuniyoshi Rebelatto[2], Paulo Roberto Slud Brofman[2], José Ademar Villanova Junior[1]
Affiliations expand

- PMID: 34425413

- DOI: 10.1016/j.rvsc.2021.08.006

Abstract

The use of regenerative medicine for pets has been growing in recent years, and an increasing number of studies have contributed to the widespread use of cell therapies in clinical veterinary medicine. Mesenchymal stem cells (MSCs) can be isolated from different sources such as dental pulp and umbilical cord. Aiming safety and reproducibility of cell therapy in clinical practice by using sources easily obtained that are usually discarded, this study isolated, characterized, and evaluated the proliferation and colony formation potential of canine dental pulp-derived mesenchymal stem cells (cDPSCs) and canine umbilical cord tissue (cUCSCs). Three samples from each source were collected, isolated, and cultured. MSCs were differentiated into three lineages and quantified by spectrophotometry. For immunophenotypic characterization, antibodies were used to analyze the expression of cell surface markers, and 7-AAD and Annexin-V were used to analyze cell viability and apoptosis, respectively. For the clonogenic assay, cells were cultured, the colonies were stained, and counted. For the proliferation assay, the cells were plated in flasks for three days and added EdU nucleoside. cDPSCs and cUCSCs showed plastic adherence and fibroblastic morphology after cultivation. Both sources showed differentiation potential and showed CD29 and CD44 positivity and CD14, CD45, CD34 and HLA-DR negativity, and low mortality and apoptosis rates. There was no difference in proliferation rates between sources. Overall, although cUCSCs had a higher number of colony-forming units than cDPSCs, both sources presented MSCs characteristics and can be used safely as alternative sources in cell therapy.

Expert Rev Anticancer Ther
.
. 2021 Aug 27;1-26.
doi: 10.1080/14737140.2021.1919090. Online ahead of print.

Antitumor effects of the multi-target tyrosine kinase inhibitor cabozantinib: a comprehensive review of the preclinical evidence

Matteo Santoni[1], Roberto Iacovelli[2], Valentina Colonna[3], Stephan Klinz[4], Giorgio Mauri[5], Marianna Nuti[6]
Affiliations expand

- PMID: 34445927

- DOI: 10.1080/14737140.2021.1919090

Abstract

Introduction: Altered receptor tyrosine kinase (RTK) signaling contributes to tumorigenesis and suppression of immune-mediated destruction of cancer cells. Cabozantinib is an oral tyrosine kinase inhibitor that inhibits several RTKs involved in tumorigenesis, and is approved for the treatment of patients with progressive metastatic medullary thyroid cancer, advanced renal cell carcinoma, and hepatocellular carcinoma that has been previously treated with sorafenib.

Areas covered: We present an up-to-date evaluation of preclinical evidence for RTK inhibition with cabozantinib, specifically VEGFR, MET, KIT, RET, AXL, FLT3, and associated antitumor effects. Preclinical investigations of cabozantinib in combination with other anticancer drugs are also reviewed.

Expert opinion: Preclinical evidence shows that cabozantinib has antitumor activity against various cancer cells and exhibits synergy with other anticancer agents, including immune checkpoint inhibitors and hormone receptor or metabolic pathway inhibitors. Further optimization of cabozantinib treatment requires the identification of biomarkers of response and resistance, and exploration of complementary drug targets. Investigation of mechanisms of adaptive resistance, such as epithelial to mesenchymal transition (cancer intrinsic) and immunomodulation by the tumor microenvironment (cancer extrinsic), as well as identification of novel drug targets based on characterization of cancer stem cell metabolomic phenotypes, appear to be promising approaches.

Keywords: Antitumor; RTK; anticancer; cabozantinib; combination therapy; preclinical; receptor tyrosine kinase; review; synergistic; tyrosine kinase inhibitor.