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Stem Cells Transl Med

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Trends in Mesenchymal Stem Cell Clinical Trials 2004-2018: Is Efficacy Optimal in a Narrow Dose Range?

[Maciej Kabat](#), [Ivan Bobkov](#) ... [Martin Grumet](#)expand

- PMID: 31804767
- DOI: [10.1002/sctm.19-0202](https://doi.org/10.1002/sctm.19-0202)

Abstract

Numbers of clinical trials using mesenchymal stem cells (MSCs) have increased since 2008 but this trend slowed in the past several years and dropped precipitously in 2018. Previous reports have analyzed MSC clinical trials by disease, phase, cell source, country of origin, and trial initiation date, all of which can be downloaded directly from ClinicalTrials.gov. We have extended analyses to a larger group of 914 MSC trials reported through 2018. To search for potential factors that may influence the design of new trials, we extracted data on routes of administration and dosing from individual ClinicalTrials.gov records as this information cannot be downloaded directly from the database. Intravenous (IV) injection is the most common, least invasive and most reproducible method, accounting for 43% of all trials. The median dose for IV delivery is 100 million MSCs/patient/dose. Analysis of all trials using IV injection that reported positive outcomes indicated minimal effective doses (MEDs) ranging from 70 to 190 million MSCs/patient/dose in 14/16 trials with the other two trials administering much higher doses of at least 900 million cells. Dose-response data showing differential efficacy for improved outcomes were reported in only four trials, which indicated a narrower MED range of 100-150 million MSCs/patient with lower and higher IV doses being less effective. The results suggest that it may be critical to determine MEDs in early trials before proceeding with large clinical trials.

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, 7, 338

Influence of Platelet Lysate on 2D and 3D Amniotic Mesenchymal Stem Cell Cultures

[Markus Pasztorek](#), [Eva Rossmannith](#) ... [Michael B Fischer](#) [expand](#)

- PMID: 31803733
- PMCID: [PMC6873824](#)
- DOI: [10.3389/fbioe.2019.00338](#)

Abstract

The mechanobiological behavior of mesenchymal stem cells (MSCs) in two- (2D) or three-dimensional (3D) cultures relies on the formation of actin filaments which occur as stress fibers and depends on mitochondrial dynamics involving vimentin intermediate filaments. Here we investigate whether human platelet lysate (HPL), that can potentially replace fetal bovine serum for clinical-scale expansion of functional cells, can modulate the stress fiber formation, alter mitochondrial morphology, change membrane elasticity and modulate immune regulatory molecules IDO and GARP in amnion derived MSCs. We can provide evidence that culture supplementation with HPL led to a reduction of stress fiber formation in 2D cultured MSCs compared to a conventional growth medium (MSCGM). 3D MSC cultures, in contrast, showed decreased actin concentrations independent of HPL supplementation. When stress fibers were further segregated by their binding to focal adhesions, a reduction in ventral stress fibers was observed in response to HPL in 2D cultured MSCs, while the length of the individual ventral stress fibers increased. Dorsal stress fibers or transverse arcs were not affected. Interestingly, ventral stress fiber formation did not correlate with membrane elasticity. 2D cultured MSCs did not show differences in the Young's modulus when propagated in the presence of HPL and further cultivation to passage 3 also had no effect on membrane elasticity. In addition, HPL reduced the mitochondrial mass of 2D cultured MSCs while the mitochondrial mass in 3D cultured MSCs was low initially. When mitochondria were segregated into punctuate, rods and networks, a cultivation-induced increase in punctuate and network mitochondria was observed in 2D cultured MSCs of passage 3. Finally, mRNA and protein expression of the immunomodulatory molecule IDO relied on stimulation of 2D culture MSCs with pro-inflammatory cytokines IFN- γ and TNF- α with no effect upon HPL supplementation. GARP mRNA and surface expression was constitutively expressed and did not respond to HPL

supplementation or stimulation with IFN- γ and TNF- α . In conclusion, we can say that MSCs cultivated in 2D and 3D are sensitive to medium supplementation with HPL with changes in actin filament formation, mitochondrial dynamics and membrane elasticity that can have an impact on the immunomodulatory function of MSCs.

Int J Nanomedicine

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A Nanodrug Consisting Of Doxorubicin And Exosome Derived From Mesenchymal Stem Cells For Osteosarcoma Treatment In Vitro

[Hongxiang Wei](#)[#], [Jinyuan Chen](#)[#] ... [Jianhua Lin](#)expand

- PMID: 31802872
- PMCID: [PMC6830377](#)
- DOI: [10.2147/IJN.S218988](#)

Abstract

Purpose: The primary goal of the present study was to develop the nano-drug consisting of doxorubicin and exosome derived from mesenchymal stem cells, and to explore its effect on osteosarcoma in vitro.

Methods: The exosomes were isolated from bone marrow MSCs (BM-MSCs) by an Exosome Isolation Kit. The exosome-loaded doxorubicin (Exo-Dox) was prepared by mixing exosome with Dox-HCl, desalinizing with triethylamine and then dialyzing against PBS overnight. The nanoparticle tracking analysis (NTA) and transmission electron microscope (TEM) were used to characterize of the exosome and Exo-Dox. The cytotoxicity of Exo-Dox was determined by CCK-8 assay. Further, the cellular uptake of different drugs was analyzed using inverted fluorescence microscope and flow cytometry.

Results: The typical exosome structures can be observed by TEM. After loading with doxorubicin, its size is larger than free exosome. Compared with the free Dox, the prepared Exo-Dox showed enhanced cellular uptake efficiency and anti-tumor effect in osteosarcoma MG63 cell line but low cytotoxicity in myocardial H9C2 cell line.

Conclusion: The prepared Exo-Dox could be used as an excellent chemotherapeutic drug for treatment of osteosarcoma in vitro. Considering the tumor-homing feature of BM-MSCs, the Exo-Dox may be a good candidate for targeted osteosarcoma treatment in future study.

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Differences in Osteogenic Induction of Human Mesenchymal Stem Cells Between a Tailored 3D Hybrid Scaffold and a 2D Standard Culture

[Samuele M Dozio](#), [Monica Montesi](#) ... [Silvia Panseri](#)expand

- PMID: 31802234
- DOI: [10.1007/s10856-019-6346-3](https://doi.org/10.1007/s10856-019-6346-3)

Abstract

Many medical-related scientific discoveries arise from trial-error patterns where the processes involved must be refined and modified continuously before any product could be able to reach the final costumers. One of the elements affecting negatively these processes is the inaccuracy of two-dimension (2D) standard culture systems, carried over in plastic plates or similar, in replicating complex environments and patterns. Consequently, animal tests are required to validate every in vitro finding, at the expenses of more funds and ethical issues. A possible solution relies in the implementation of three-dimension (3D) culture systems as a fitting gear between the 2D tests and in vivo tests, aiming to reduce the negative in vivo outcomes. These 3D structures are depending from the comprehension of the extracellular matrix (ECM) and the ability to replicate it in vitro. In this article a comparison of efficacies between these two culture systems was taken as

subject, human mesenchymal stem cells (hMSCs) was utilized and a hybrid scaffold made by a blend of chitosan, gelatin and biomineralized gelatin was used for the 3D culture system.

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Adult Stem Cells for Bone Regeneration and Repair

[Maria Rosa Iaquina](#), [Elisa Mazzoni](#) ... [Fernanda Martini](#)expand

- PMID: 31799249
- PMCID: [PMC6863062](#)
- DOI: [10.3389/fcell.2019.00268](#)

Abstract

The regeneration of bone fractures, resulting from trauma, osteoporosis or tumors, is a major problem in our super-aging society. Bone regeneration is one of the main topics of concern in regenerative medicine. In recent years, stem cells have been employed in regenerative medicine with interesting results due to their self-renewal and differentiation capacity. Moreover, stem cells are able to secrete bioactive molecules and regulate the behavior of other cells in different host tissues. Bone regeneration process may improve effectively and rapidly when stem cells are used. To this purpose, stem cells are often employed with biomaterials/scaffolds and growth factors to accelerate bone healing at the fracture site. Briefly, this review will describe bone structure and the osteogenic differentiation of stem cells. In addition, the role of mesenchymal stem cells for bone repair/regrowth in the tissue engineering field and their recent progress in clinical applications will be discussed.

FEBS Open Bio

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Dexamethasone Promotes Mesenchymal Stem Cell Apoptosis and Inhibits Osteogenesis by Disrupting Mitochondrial Dynamics

[Liang Ma](#), [Xiaobo Feng](#) ... [Cao Yang](#)expand

- PMID: 31788976
- DOI: [10.1002/2211-5463.12771](https://doi.org/10.1002/2211-5463.12771)

Abstract

Long-term or heavy use of glucocorticoids (GC) can cause severe necrosis of the femoral head, but the underlying mechanisms are still unclear. Recent studies have found that mitochondrial dynamics play an important role in femoral head necrosis. Here, we investigated the effect of dexamethasone on the mitochondrial function of mesenchymal stem cells (MSCs). We observed that high concentrations of dexamethasone (10^{-6} mol/L) decreased cell activity, promoted apoptosis, elevated levels of reactive oxygen species (ROS), and disrupted mitochondrial dynamics. Furthermore, dexamethasone (10^{-6} mol/L) inhibited osteogenesis of stem cells and promoted adipogenesis. These findings may facilitate greater understanding of the adverse effects of dexamethasone on the femoral head.