ML 29-18 (26/08/2018)

Cytotherapy. 2018 Aug 6. pii: S1465-3249(18)30555-3. doi: 10.1016/j.jcyt.2018.06.013. [Epub ahead of print]

In vitro and in vivo discrepancy in inducing apoptosis by mesenchymal stromal cells delivering membrane-bound tumor necrosis factor-related apoptosis inducing ligand in osteosarcoma pre-clinical models.

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Author information

Abstract

BACKGROUND:

Osteosarcoma (OS) is the most frequent pediatric malignant bone tumor. OS patients have not seen any major therapeutic progress in the last 30 years, in particular in the case of metastatic disease, which requires new therapeutic strategies. The pro-apoptotic cytokine Tumor necrosis factor (TNF)-Related Apoptosis Inducing Ligand (TRAIL) can selectively kill tumor cells while sparing normal cells, making it a promising therapeutic tool in several types of cancer. However, many OS cell lines appear resistant to recombinant human (rh)TRAIL-induced apoptosis. We, therefore, hypothesized that TRAIL presentation at the membrane level of carrier cells might overcome this resistance and trigger apoptosis.

METHODS:

To address this, human adipose mesenchymal stromal cells (MSCs) transfected in a stable manner to express membrane-bound full-length human TRAIL (mbTRAIL) were co-cultured with several human OS cell lines.

RESULTS:

This induced apoptosis by cell-to-cell contact even in cell lines initially resistant to rhTRAIL. In contrast, mbTRAIL delivered by MSCs was not able to counteract tumor progression in this OS orthotopic model.

DISCUSSION:

This was partly due to the fact that MSCs showed a potential to support tumor development. Moreover, the expression of mbTRAIL did not show caspase activation in adjacent tumor cells.

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Functional impairment of MSC induced by transient warming events: Correlation with loss of adhesion and altered cell size.

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Author information

Abstract

BACKGROUND:

We recently showed that transient warming effects decreased the functional and adhesion properties of mesenchymal stromal cells (MSC) while post-thaw viability remained high. In an attempt to better predict functional impairment of cryopreserved MSC, we further analysed the correlation between viability, immunosuppressive activity and adhesion of cells exposed or not to warming events.

METHODS:

MSC prepared from six umbilical cords were frozen to -130°C and immediately transferred in a dry ice container or exposed to room temperature for 2 to 10 min (warming events) prior to storage in liquid nitrogen. Viability, functionality (inhibition of T-cell proliferation), adhesion and expression of various integrins were evaluated.

RESULTS:

The monotonic loss of functional activity with time was proportional to the length of warming events to which MSC were subjected and correlated with the monotonic loss of adhesion capacity. In contrast, post-thaw viability assessment did not predict functional impairment. Interestingly, flow cytometry analyses revealed the emergence of a FSC^{low} population present in the viable cell fraction of freshly thawed MSC, which displayed poor adhesion capacity and expressed low levels of integrin β5. The prevalence of this FSC^{low} population increased with the length of warming events and correlated with impaired functional and adhesion properties.

DISCUSSION:

Our results reveal that loss of functional activity (4-day test) induced by transient warming events could be predicted by evaluating adhesion (2-hr test) or FSC profile (10-min test) of MSC immediately post-thaw. These observations could lead to the development of surrogate tests for rapidly assessing the functional quality of cryopreserved MSC.

Lab Invest. 2018 Aug 8. doi: 10.1038/s41374-018-0110-z. [Epub ahead of print]

The effect of mesenchymal stem cells' secretome on lung cancer progression is contingent on their origin: primary or metastatic niche.

Attar-Schneider O[1,2,3], Drucker L[4,5], Gottfried M[6,7,5].
Author information

Abstract

The fatality of non-small-cell lung cancer (NSCLC) and the role of the cancer microenvironment in its resistance to therapy are long recognized. Accumulating data allocate a significant role for mesenchymal stem cells (MSCs) in the malignant environment. Previously, we have demonstrated that MSCs from NSCLC metastatic bone marrow (BM) niche deleteriously affected NSCLC cells. Here, we have decided to examine the effect of MSCs from the primary niche of the lung (healthy or adjacent to tumor) on NSCLC phenotype. We cultured NSCLC cell lines with healthy/NSCLC lung-MSCs conditioned media (secretome) and showed elevation in cells' MAPKs and translation initiation signals, proliferation, viability, death, and migration. We also established enhanced autophagy and epithelial to

mesenchymal transition processes. Moreover, we observed that MSCs from tumor adjacent sites (pathological niche) exhibited a more profound effect than MSCs from healthy lung tissue. Our findings underscore the capacity of the lung-MSCs to modulate NSCLC phenotype. Interestingly, both tumor adjacent (pathological) and distant lung-MSCs (healthy) promoted the NSCLC's TI, proliferation, migration, and epithelial to mesenchymal transition, yet the pathological MSCs displayed a greater affect. In conclusion, by comparing the effects of normal lung-MSCs, NSCLC adjacent MSCs, and BM-MSCs, we have established that the primary and metastatic niches display opposite and critical effects that promote the cancerous systemic state. Specifically, the primary site MSCs promote the expansion of the malignant clone and its dispersion, whereas the metastatic site MSCs facilitates the cells re-seeding. We suggest that sabotaging the cross-talk between MSCs and NSCLC affords effective means to inhibit lung cancer progression and will require different targeting strategies in accordance with niche/disease stage.

Biofabrication. 2018 Aug 8. doi: 10.1088/1758-5090/aad8d9. [Epub ahead of print]

Biofabrication of human articular cartilage: a path towards the development of a clinical treatment.

Onofrillo C[1], Duchi S[2], O'Connell C[3], Blanchard R[2], O'Connor AJ[4], Scott M[5], Wallace GG[6], Choong P[7], Di Bella C[8].
Author information

Abstract

Cartilage injuries cause pain and loss of function, and if severe may result in osteoarthritis.
 3D bioprinting is now a tangible option for the delivery of bioscaffolds capable of regenerating the deficient cartilage tissue. Our team has developed a handheld device, the Biopen, to allow in situ additive manufacturing during surgery. Given its ability to extrude in a core/shell manner, the Biopen can preserve cell viability during the biofabrication process, and it is currently the only biofabrication tool tested as a surgical instrument in a sheep model using homologous stem cells.
 As a necessary step toward the development of a clinically relevant protocol, we aimed to demonstrate that our handheld extrusion device can successfully be used for the biofabrication of human cartilage. Therefore this study is a required step for the development of a surgical treatment in human patients.
 In this work we specifically used human derived mesenchymal stem cells (hADSCs), harvested from the Infra-Patellar Fat Pad of donor patients affected by Osteoarthritis, to also prove that they can be utilized as the source of cells for the future clinical application.
 With the Biopen, we generated bioscaffolds made of hADSCs laden in Gelatin Methacrylate (GelMa), hyaluronic acid methacrylate (HAMa) and cultured in the presence of chondrogenic stimuli for eight weeks in vitro.
 A comprehensive characterisation including gene and protein expression analyses, immunohistology, confocal microscopy, second harmonic generation, light sheet imaging, and mechanical unconfined compression demonstrated that our strategy resulted in human hyaline-like cartilage formation.
 Our in situ biofabrication approach represents an innovation with important implications for customizing cartilage repair in patients with cartilage injuries and osteoarthritis. &#13.

ACS Omega. 2018 Jul 31;3(7):8097-8103. doi: 10.1021/acsomega.8b00908. Epub 2018 Jul 19.

Efficient Route to Label Mesenchymal Stromal Cell-Derived Extracellular Vesicles.

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Author information

Abstract

Recent research results report that extracellular vesicles (EVs) have a central role in both physiological and pathological processes involving intercellular communication. Herein, a simple EVs labeling procedure based on the metabolic labeling of secreting cells (mesenchymal stroma cells, MSCs) with a fluorescein-containing bio-orthogonal dye is described. This procedure was carried out by incubating cells for 72 h with tetraacetylated *N*-azidoacetyl-d-mannosamine (Ac_4ManNAz), a modified sugar containing an azido group that, upon incorporation on the external surface of the cytoplasmatic cell membrane, is specifically conjugated with cyclooctyne-modified fluorescein isothiocyanate (ADIBO-FITC). MSCs released fluorescent EVs did not need any further purification. Finally, cellular uptake and tracking of the fluorescein-labeled EVs were successfully assessed by targeting experiments with MSCs. The method appears of general applicability and it may be very useful opening new horizon on diagnostic and therapeutic protocols exploiting EVs.

Int J Mol Sci. 2018 Aug 7;19(8). pii: E2312. doi: 10.3390/ijms19082312.

CTLA-4 Mediates Inhibitory Function of Mesenchymal Stem/Stromal Cells.

Gaber T[1,2], Schönbeck K[3,4], Hoff H[5], Tran CL[6,7], Strehl C[8,9], Lang A[10,11], Ohrndorf S[12], Pfeiffenberger M[13,14], Röhner E[15], Matziolis G[16], Burmester GR[17,18], Buttgereit F[19,20], Hoff P[21,22,23,24].
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Abstract

Mesenchymal stem/stromal cells (MSCs) are stem cells of the connective tissue, possess a plastic phenotype, and are able to differentiate into various tissues. Besides their role in tissue regeneration, MSCs perform additional functions as a modulator or inhibitor of immune responses. Due to their pleiotropic function, MSCs have also gained therapeutic importance for the treatment of autoimmune diseases and for improving fracture healing and cartilage regeneration. However, the therapeutic/immunomodulatory mode of action of MSCs is largely unknown. Here, we describe that MSCs express the inhibitory receptor CTLA-4 (cytotoxic T lymphocyte antigen 4). We show that depending on the environmental conditions, MSCs express different isoforms of CTLA-4 with the secreted isoform (sCTLA-4) being the most abundant under hypoxic conditions. Furthermore, we demonstrate that the immunosuppressive function of MSCs is mediated mainly by the secretion of CTLA-4. These findings open new ways for treatment when tissue regeneration/fracture healing is difficult.

Stem Cells Transl Med. 2018 Aug 1. doi: 10.1002/sctm.18-0024. [Epub ahead of print]

Concise Review: Mesenchymal Stem Cell-Based Drug Delivery: The Good, the Bad, the Ugly, and the Promise.

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Abstract

The development of mesenchymal stem cells (MSCs) as cell-based drug delivery vectors for numerous clinical indications, including cancer, has significant promise. However, a considerable challenge for effective translation of these approaches is the limited tumor tropism and broad biodistribution observed using conventional MSCs, which raises concerns for toxicity to nontarget peripheral tissues (i.e., the bad). Consequently, there are a variety of synthetic engineering platforms in active development to improve tumor-selective targeting via increased homing efficiency and/or specificity of drug activation, some of which are already being evaluated clinically (i.e., the good). Unfortunately, the lack of robust quantification and widespread adoption of standardized methodologies with high sensitivity and resolution has made accurate comparisons across studies difficult, which has significantly impeded progress (i.e., the ugly). Herein, we provide a concise review of active and passive MSC homing mechanisms and biodistribution postinfusion; in addition to in vivo cell tracking methodologies and strategies to enhance tumor targeting with a focus on MSC-based drug delivery strategies for cancer therapy. Stem Cells

J Transl Med. 2018 Jul 31;16(1):213. doi: 10.1186/s12967-018-1591-7.

Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: long-term follow up of a multicenter randomized controlled clinical trial (phase I/II).

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Author information

Abstract

BACKGROUND:

Mesenchymal stromal cells (MSCs) are a promising option to treat knee osteoarthritis (OA). Their safety and usefulness have been reported in several short-term clinical trials but less information is available on the long-term effects of MSC in patients with osteoarthritis. We have evaluated patients included in our previous randomized clinical trial (CMM-ART, NCT02123368) to determine their long-term clinical effect.

MATERIALS:

A phase I/II multicenter randomized clinical trial with active control was conducted between 2012 and 2014. Thirty patients diagnosed with knee OA were randomly assigned to Control group, intraarticularly administered hyaluronic acid alone, or to two treatment groups, hyaluronic acid together with 10×10^6 or

100×10^6 cultured autologous bone marrow-derived MSCs (BM-MSCs), and followed up for 12 months. After a follow up of 4 years adverse effects and clinical evolution, assessed using VAS and WOMAC scorings are reported.

RESULTS:

No adverse effects were reported after BM-MSCs administration or during the follow-up. BM-MSCs-administered patients improved according to VAS, median value (IQR) for Control, Low-dose and High-dose groups changed from 5 (3, 7), 7 (5, 8) and 6 (4, 8) to 7 (6, 7), 2 (2, 5) and 3 (3, 4), respectively at the end of follow up (Low-dose vs Control group, p = 0.01; High-dose vs Control group, p = 0.004). Patients receiving BM-MSCs also improved clinically according to WOMAC. Control group showed an increase median value of 4 points (- 11;10) while Low-dose and High-dose groups exhibited values of - 18 (- 28;- 9) and - 10 (- 21;- 3) points, respectively (Low-dose vs Control group p = 0.043). No clinical differences between the BM-MSCs receiving groups were found.

CONCLUSIONS:

Single intraarticular injection of in vitro expanded autologous BM-MSCs is a safe and feasible procedure that results in long-term clinical and functional improvement of knee OA.

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Front Med. 2018 Jul 30. doi: 10.1007/s11684-018-0627-y. [Epub ahead of print]

Mesenchymal stem cells and immune disorders: from basic science to clinical transition.

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Author information

Abstract

As a promising candidate seed cell type in regenerative medicine, mesenchymal stem cells (MSCs) have attracted considerable attention. The unique capacity of MSCs to exert a regulatory effect on immunity in an autologous/allergenic manner makes them an attractive therapeutic cell type for immune disorders. In this review, we discussed the current knowledge of and advances in MSCs, including its basic biological properties, i.e., multilineage differentiation, secretome, and immunomodulation. Specifically, on the basis of our previous work, we proposed three new concepts of MSCs, i.e., "subtotipotent stem cell" hypothesis, MSC system, and "Yin and Yang" balance of MSC regulation, which may bring new insights into our understanding of MSCs. Furthermore, we analyzed data from the Clinical Trials database (http://clinicaltrials.gov) on registered clinical trials using MSCs to treat a variety of immune diseases, such as graft-versus-host disease, systemic lupus erythematosus, and multiple sclerosis. In addition, we highlighted MSC clinical trials in China and discussed the challenges and future directions in the field of MSC clinical application.

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Eur J Haematol. 2018 Aug 6. doi: 10.1111/ejh.13158. [Epub ahead of print]

Second-Line Treatment for Acute Graft-Versus-Host Disease with Mesenchymal Stromal Cells: A decision model.

Thielen FW[1], Blommestein HM[1,2], Oosten LEM[3], Calkoen FG[4], Lankester AC[4], Zwaginga JJ[3,5], Le Blanc K[6], Redondo A[7], Sánchez-Guijo F[7], Algeri M[8], Locatelli F[8], Fibbe WE[3], Uyl-de Groot CA[1].
Author information

Abstract

OBJECTIVE:

No standard second-line treatment exists for acute graft-versus-host disease steroid-refractory (SR-aGvHD) and long-term outcomes remain poor. Mesenchymal stromal cells (MSC) have been evaluated as treatment but no disease model (DM) exists that integrates and extrapolates currently available evidence. The aim to develop such a DM to describe the natural history of SR-aGvHD and to predict long-term outcomes.

METHOD:

The DM was developed in collaboration with experts in haematology-oncology. Subsequently, a model simulation was run. Input parameters for transition and survival estimates were informed by published data of clinical trials on MSC treatment for SR-aGvHD. Parametric distributions were used to estimate long-term survival rates after MSCs.

RESULTS:

The newly developed DM is a cohort model that consists of eight health states. For the model simulation, we obtained data on 327 patients from 14 published phase II trials. Due to limited evidence, DM structure was simplified and several assumptions had to be made. Median overall survival was 3.2 years for complete response and 0.5 years for no complete response.

CONCLUSION:

The DM provides a comprehensive overview on the second-line treatment pathway for aGvHD and enables long-term predictions that can be used to perform a cost-effectiveness analysis comparing any treatment for SR-aGvHD.

Cytotherapy. 2018 Jul 31. pii: S1465-3249(18)30542-5. doi: 10.1016/j.jcyt.2018.05.011. [Epub ahead of print]

Human mesenchymal stromal cells do not promote recurrence of soft tissue sarcomas in mouse xenografts after radiation and surgery.

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Author information

Abstract

BACKGROUND:

Mesenchymal stromal cells (MSCs) promote wound healing, including after radiotherapy (RT) and surgery. The use of MSCs in regenerative medicine in the context of malignancy, such as to enhance wound healing post-RT/surgery in patients with soft tissue sarcomas (STSs), requires safety validation.

The aim of this study was to determine the effects of human MSCs on STS growth in vitro and local recurrence and metastasis in vivo.

METHODS:

Human primary STS and HT-1080 fibrosarcoma lines were transduced to express luciferase/eGFP (enhanced green fluorescent protein). Sarcoma cells were co-cultured or co-injected with bone marrow-derived MSCs for growth studies. Xenograft tumor models were established with STS lines in NOD/SCID/γ_c^{null} mice. To emulate a clinical scenario, subcutaneous tumors were treated with RT/surgery prior to MSC injection into the tumor bed. Local and distant tumor recurrence was studied using histology and bioluminescence imaging.

RESULTS:

MSCs did not promote STS proliferation upon co-culture in vitro, which was consistent among MSCs from different donors. Co-injection of MSCs with sarcoma cells in mice exhibited no significant tumor-stimulating effect, compared with control mice injected with sarcoma cells alone. MSC administration after RT/surgery had no effect on local recurrence or metastasis of STS.

DISCUSSION:

These studies are important for the establishment of a safety profile for MSC administration in patients with STS. Our data suggest that MSCs are safe in STS management after standard of care RT/surgery, which can be further investigated in early-phase clinical trials to also determine the efficacy of MSCs in reducing morbidity and to mitigate wound complications in these patients.