BMC Vet Res. 2018 Jun 25;14(1):202. doi: 10.1186/s12917-018-1527-8.

Allogeneic mesenchymal stem cells improve the wound healing process of sheep skin.

Martinello T[1], Gomiero C[1], Perazzi A[2], Iacopetti I[2], Gemignani F[2], DeBenedictis GM[2], Ferro S[1], Zuin M[3], Martines E[3], Brun P[4], Maccatrozzo L[1], Chiers K[5], Spaas JH[6], Patruno M[7].

Author information

Abstract

BACKGROUND:

Skin wound healing includes a system of biological processes, collectively restoring the integrity of the skin after injury. Healing by second intention refers to repair of large and deep wounds where the tissue edges cannot be approximated and substantial scarring is often observed. The objective of this study was to evaluate the effects of mesenchymal stem cells (MSCs) in second intention healing using a surgical wound model in sheep. MSCs are known to contribute to the inflammatory, proliferative, and remodeling phases of the skin regeneration process in rodent models, but data are lacking for large animal models. This study used three different approaches (clinical, histopathological, and molecular analysis) to assess the putative action of allogeneic MSCs at 15 and 42 days after lesion creation.

RESULTS:

At 15 days post-lesion, the wounds treated with MSCs showed a higher degree of wound closure, a higher percentage of re-epithelialization, proliferation, neovascularization and increased contraction in comparison to a control group. At 42 days, the wounds treated with MSCs had more mature and denser cutaneous adnexa compared to the control group. The MSCs-treated group showed an absence of inflammation and expression of CD3+ and CD20+. Moreover, the mRNA expression of hair-keratine (hKER) was observed in the MSCs-treated group 15 days after wound creation and had increased significantly by 42 days post-wound creation. Collagen1 gene (Col1α1) expression was also greater in the MSCs-treated group compared to the control group at both days 15 and 42.

CONCLUSION:

Peripheral blood-derived MSCs may improve the quality of wound healing both for superficial injuries and deep lesions. MSCs did not induce an inflammatory response and accelerated the appearance of granulation tissue, neovascularization, structural proteins, and skin adnexa.

Stem Cells Int. 2018 May 27;2018:9863194. doi: 10.1155/2018/9863194. eCollection 2018.

Extracellular Vesicles: A New Prospective in Crosstalk between Microenvironment and Stem Cells in Hematological Malignancies.

Laurenzana I[1], Lamorte D[1], Trino S[1], De Luca L[1], Ambrosino C[2], Zoppoli P[1], Ruggieri V[1], Del Vecchio L[3,4], Musto P[5], Caivano A[1], Falco G[6,7].
Author information
Abstract

The bone marrow (BM) microenvironment in hematological malignancies (HMs) comprises heterogeneous populations of neoplastic and nonneoplastic cells. Cancer stem cells (CSCs), neoplastic cells, hematopoietic stem cells (HSCs), and mesenchymal stromal/stem cells (MSCs) are all components of this microenvironment. CSCs are the HM initiators and are associated with neoplastic growth and drug resistance, while HSCs are able to reconstitute the entire hematopoietic system; finally, MSCs actively support hematopoiesis. In some HMs, CSCs and neoplastic cells compromise the normal development of HSCs and perturb BM-MSCs. In response, "reprogrammed" MSCs generate a favorable environment to support neoplastic cells. Extracellular vesicles (EVs) are an important cell-to-cell communication type in physiological and pathological conditions. In particular, in HMs, EV secretion participates to unidirectional and bidirectional interactions between neoplastic cells and BM cells. The transfer of EV molecular cargo triggers different responses in target cells; in particular, malignant EVs modify the BM environment in favor of neoplastic cells at the expense of normal HSCs, by interfering with antineoplastic immunity and participating in resistance to treatment. Here, we review the role of EVs in BM cell communication in physiological conditions and in HMs, focusing on the effects of BM niche EVs on HSCs and MSCs.

Am J Sports Med. 2018 Jun 1:363546518781825. doi: 10.1177/0363546518781825. [Epub ahead of print]

First-in-Human Pilot Study of Implantation of a Scaffold-Free Tissue-Engineered Construct Generated From Autologous Synovial Mesenchymal Stem Cells for Repair of Knee Chondral Lesions.

Shimomura K[1], Yasui Y[1], Koizumi K[1], Chijimatsu R[1], Hart DA[1], Yonetani Y[1], Ando W[1], Nishii T[1], Kanamoto T[1], Horibe S[1], Yoshikawa H[1], Nakamura N[1], Sakaue M[1], Sugita N[1], Moriguchi Y[1].

Author information
Abstract

BACKGROUND:

Articular cartilage has limited healing capacity, owing in part to poor vascularity and innervation. Once injured, it cannot be repaired, typically leading to high risk for developing osteoarthritis. Thus, cell-based and/or tissue-engineered approaches have been investigated; however, no approach has yet achieved safety and regenerative repair capacity via a simple implantation procedure.

PURPOSE:

To assess the safety and efficacy of using a scaffold-free tissue-engineered construct (TEC) derived from autologous synovial membrane mesenchymal stem cells (MSCs) for effective cartilage repair.

STUDY DESIGN:

Case series; Level of evidence, 4.

METHODS:

Five patients with symptomatic knee chondral lesions (1.5-3.0 cm^2) on the medial femoral condyle, lateral femoral condyle, or femoral groove were included. Synovial MSCs were isolated from arthroscopic biopsy specimens and cultured to develop a TEC that matched the lesion size. The TECs were then implanted into chondral defects without fixation and assessed up to 24 months postoperatively. The primary outcome was the safety of the procedure. Secondary outcomes were self-assessed clinical scores, arthroscopy, tissue biopsy, and magnetic resonance image-based estimation of morphologic and compositional quality of the repair tissue.

RESULTS:

No adverse events were recorded, and self-assessed clinical scores for pain, symptoms, activities of daily living, sports activity, and quality of life were significantly improved at 24 months after surgery. Secure defect filling was confirmed by second-look arthroscopy and magnetic resonance imaging in all cases. Histology of biopsy specimens indicated repair tissue approaching the composition and structure of hyaline cartilage.

CONCLUSION:

Autologous scaffold-free TEC derived from synovial MSCs may be used for regenerative cartilage repair via a sutureless and simple implantation procedure. Registration: 000008266 (UMIN Clinical Trials Registry number).

Stem Cells. 2018 Jul 3. doi: 10.1002/stem.2853. [Epub ahead of print]

Hypoxic Preconditioning of Mesenchymal Stem Cells with Subsequent Spheroid Formation Accelerates Repair of Segmental Bone Defects.

Ho SS[1], Hung BP[1], Heyrani N[2], Lee MA[2], Leach JK[1,2].
Author information

Abstract

Cell-based approaches for musculoskeletal tissue repair are limited by poor cell survival and engraftment. Short-term hypoxic preconditioning of mesenchymal stem cells (MSCs) can prolong cell viability in vivo, while the aggregation of MSCs into spheroids increases cell survival, trophic factor secretion, and tissue formation in vivo. We hypothesized that preconditioning MSCs in hypoxic culture before spheroid formation would increase cell viability, proangiogenic potential, and resultant bone repair compared with that of individual MSCs. Human MSCs were preconditioned in 1% O_2 in monolayer culture for 3 days (PC3) or kept in ambient air (PC0), formed into spheroids of increasing cell density, and then entrapped in alginate hydrogels. Hypoxia-preconditioned MSC spheroids were more resistant to apoptosis than ambient air controls and this response correlated with duration of hypoxia exposure. Spheroids of the highest cell density exhibited the greatest osteogenic potential in vitro and vascular endothelial growth factor (VEGF) secretion was greatest in PC3 spheroids. PC3 spheroids were then transplanted into rat critical-sized femoral segmental defects to evaluate their

potential for bone healing. Spheroid-containing gels induced significantly more bone healing compared with gels containing preconditioned individual MSCs or acellular gels. These data demonstrate that hypoxic preconditioning represents a simple approach for enhancing the therapeutic potential of MSC spheroids when used for bone healing

Histol Histopathol. 2018 Jul 3:18018. doi: 10.14670/HH-18-018. [Epub ahead of print]

PRP and MSCs on tenocytes artificial wound healing: an in vitro study comparing fresh and frozen PRP.

Veronesi F[1], Pagani S[2], Torricelli P[1], Filardo G[3], Cavallo C[4], Grigolo B[4], Fini M[1].
Author information

Abstract

Evolutionary medicine has proven helpful to understand the origin of human disease, e.g. in identifying causal roles of recent environmental changes impacting on human physiology (environment-phenotype mismatch). In contrast, diseases affecting only a limited number of members of a species often originate from evolutionary trade-offs for usually physiologic adaptations assuring reproductive success in the context of extrinsic threats. For example, the G1 and G2 variants of the APOL1 gene supporting control of Trypanosoma infection come with the trade-off that they promote the progression of kidney disease. In this review we extend the concept of evolutionary nephrology by discussing how the physiologic adaptations (danger responses) to tissue injury create evolutionary trade-offs that drive histopathological changes underlying acute and chronic kidney diseases. The evolution of multicellular organisms positively selected a number of danger response programs for their overwhelming benefits in assuring survival such as clotting, inflammation, epithelial healing and mesenchymal healing, i.e. fibrosis and sclerosis. Upon kidney injury these danger programs often present as pathomechanisms driving persistent nephron loss and renal failure. We explore how classic kidney disease entities involve insufficient or overshooting activation of these danger response programs for which the underlying genetic basis remains largely to be defined. Dissecting the causative and hierarchical relationships between danger programs should help to identify molecular targets to control kidney injury and to improve disease outcomes.Tendon tissue has poor regenerative capacity due to its low vascularization, cell density and extracellular matrix (ECM) production. Therefore, tendon injuries are an increasing clinical problem because of the formation of scar tissue with traditional therapies. Regenerative medicine aims at triggering a healing response through the use of biological treatments such as mesenchymal stromal cells (MSCs) and growth factors (GFs). MSCs show several advantages in tendon clinical setting, while platelet rich plasma (PRP) has gained popularity because of its high GF concentration, although its applications in the tendon clinical setting are still controversial. The aim of the present study was to evaluate a combined treatment of MSCs and PRP in an in vitro microwound model of tendon injuries. In addition, fresh and frozen PRP were compared. Single human tenocytes cultures or co-cultures with bone marrow derived MSCs (BMSCs) were set up with or without human PRP, fresh or frozen. After 24 hours of culture, it was observed that MSCs alone significantly increased tenocyte migration speed, microwound healing rate, fibronectin, collagen I and aggrecan production.

These effects were enhanced by the combination with PRP, fresh being more effective than frozen PRP. In addition, the number of MSCs and tenocytes inside the microwound was significantly increased, especially with fresh PRP. In conclusion, the combination of MSCs and PRP, especially the fresh one, increases tenocytes and MSC migration speed, as well as ECM protein production compared to the use of MSCs alone.

BMB Rep. 2018 Jul 3. pii: 4198. [Epub ahead of print]

Exosomes Derived from MicroRNA-584 Transfected Mesenchymal Stem Cells: Novel Alternative Therapeutic Vehicles for Cancer Therapy.

Kim R[1], Lee S[1], Lee J[1], Kim M[1], Kim WJ[1], Lee HW[1], Lee MY[2], Kim J[3], Chang W[1].
Author information

Abstract

Exosomes are small membranous vesicles which contain abundant RNA molecules, and are transferred from releasing cells to uptaking cells. MicroRNA (miRNA) is one of the transferred molecules affecting the adopted cells, including glioma cells. We hypothesized that mesenchymal stem cells (MSCs) can secrete exosomes loading miRNA and have important effects on the progress of gliomas. To determine these effects by treating exosomal miRNA in culture media of miRNA mimic transfected MSCs, we assessed the in vitro cell proliferation and invasion capabilities, and the expression level of relative proteins associated with cell apoptosis, growth and migration. For animal studies, the mice injected with U87 cells were exposed to exosomes derived from miRNA-584-5p transfected MSCs, to confirm the influence of exosomal miRNA on the progress of glioma. Based on our results, we propose a new targeted cancer therapy wherein exosomes derived from miRNA transfected MSCs could be used to modulate tumor progress as the anticancer vehicles.

Int J Mol Sci. 2018 Jun 30;19(7). pii: E1926. doi: 10.3390/ijms19071926.

Adipose-Derived Mesenchymal Stem Cells: Are They a Good Therapeutic Strategy for Osteoarthritis?

Damia E[1,2], Chicharro D[3,4], Lopez S[5], Cuervo B[6,7], Rubio M[8,9], Sopena JJ[10,11], Vilar JM[12,13], Carrillo JM[14,15].

Author information

Abstract

Osteoarthritis (OA) is a major cause of disability in elderly population around the world. More than one-third of people over 65 years old shows either clinical or radiological evidence of OA. There is no effective treatment for this degenerative disease, due to the limited capacity for spontaneous cartilage regeneration. Regarding the use of regenerative therapies, it has been reported that one option to restore degenerated cartilage are adipose-derived mesenchymal stem cells (ASCs). The purpose of this review is to describe and compare the efficacy of ASCs versus other therapies in OA.

METHODS:

Recent studies have shown that ASCs exert paracrine effects protecting against degenerative changes in chondrocytes. According to the above, we have carried out a review of the literature using a combination of osteoarthritis, stem cells, and regenerative therapies as keywords.

RESULTS:

Conventional pharmacological therapies for OA treatment are considered before the surgical option, however, they do not stop the progression of the disease. Moreover, total joint replacement is not recommended for patients under 55 years, and high tibia osteotomy (HTO) is a viable solution to address lower limb malalignment with concomitant OA, but some complications have been described. In recent years, the use of mesenchymal stem cells (MSCs) as a treatment strategy for OA is increasing considerably, thanks to their capacity to improve symptoms together with joint functionality and, therefore, the patients’ quality of life.

CONCLUSIONS:

ASC therapy has a positive effect on patients with OA, although there is limited evidence and little long-term follow-up.

Front Med (Lausanne). 2018 Jun 15;5:179. doi: 10.3389/fmed.2018.00179. eCollection 2018.

Stem/Stromal Cells for Treatment of Kidney Injuries With Focus on Preclinical Models.

Torres Crigna A[1], Daniele C[2], Gamez C[3], Medina Balbuena S[4], Pastene DO[4], Nardozi D[2], Brenna C[2], Yard B[4], Gretz N[2], Bieback K[1].

Author information

Abstract

Within the last years, the use of stem cells (embryonic, induced pluripotent stem cells, or hematopoietic stem cells), Progenitor cells (e.g., endothelial progenitor cells), and most intensely mesenchymal stromal cells (MSC) has emerged as a promising cell-based therapy for several diseases including nephropathy. For patients with end-stage renal disease (ESRD), dialysis or finally organ transplantation are the only therapeutic modalities available. Since ESRD is associated with a high healthcare expenditure, MSC therapy represents an innovative approach. In a variety of preclinical and clinical studies, MSC have shown to exert renoprotective properties, mediated mainly by paracrine effects, immunomodulation, regulation of inflammation, secretion of several trophic factors, and possibly differentiation to renal precursors. However, studies are highly diverse; thus, knowledge is still limited regarding the exact mode of action, source of MSC in comparison to other stem cell types, administration route and dose, tracking of cells and documentation of therapeutic efficacy by new imaging techniques and tissue visualization. The aim of this review is to provide a summary of published studies of stem cell therapy in acute and chronic kidney injury, diabetic nephropathy, polycystic kidney disease, and kidney transplantation. Preclinical studies with allogeneic or xenogeneic cell therapy were first addressed, followed by a summary of clinical trials carried out with autologous or allogeneic hMSC. Studies were analyzed with respect to source of cell type, mechanism of action etc.

Front Immunol. 2018 Jun 14;9:1359. doi: 10.3389/fimmu.2018.01359. eCollection 2018.

Long-Term Clinical and Immunological Profile of Kidney Transplant Patients Given Mesenchymal Stromal Cell Immunotherapy.

Perico N[1], Casiraghi F[1], Todeschini M[1], Cortinovis M[1], Gotti E[2], Portalupi V[2], Mister M[1], Gaspari F[1], Villa A[1], Fiori S[1], Introna M[3], Longhi E[4], Remuzzi G[1,2,5].
Author information

Abstract

We report here the long-term clinical and immunological results of four living-donor kidney transplant patients given autologous bone marrow-derived mesenchymal stromal cells (MSCs) as part of a phase 1 study focused on the safety and feasibility of this cell therapy. According to study protocols implemented over time, based on initial early safety findings, the patients were given MSC at day 7 posttransplant ($n = 2$) or at day -1 pretransplant ($n = 2$) and received induction therapy with basiliximab and low-dose rabbit anti-thymocyte globulin (RATG) or RATG alone, and were maintained on low-dose ciclosporin (CsA)/mycophenolate mofetil (MMF). All MSC-treated patients had stable graft function during the 5- to 7-year follow-up, without increased susceptibility to infections or neoplasm. In three MSC recipients, but not historical control patients, circulating memory $CD8^+$ T cell percentages remained lower than basal, coupled with persistent reduction of *ex vivo* donor-specific cytotoxicity. Two patients showed a long-lasting increase in the regulatory T cell/memory $CD8^+$ T cell ratio, paralleled by high circulating levels of naïve and transitional B cells. In one of these two patients, CsA was successfully discontinued, and currently the low-dose MMF monotherapy is on the tapering phase. The study shows that MSC therapy is safe in the long term and could promote a pro-tolerogenic environment in selected patients. Extensive immunomonitoring of MSC-treated kidney transplant recipients could help selection of patients for safe withdrawal of maintenance immunosuppressive drugs (NCT00752479 and NCT02012153).

Int J Mol Sci. 2018 Jun 26;19(7). pii: E1868. doi: 10.3390/ijms19071868.

Donor Site Location Is Critical for Proliferation, Stem Cell Capacity, and Osteogenic Differentiation of Adipose Mesenchymal Stem/Stromal Cells: Implications for Bone Tissue Engineering.

Reumann MK[1], Linnemann C[2], Aspera-Werz RH[3], Arnold S[4], Held M[5,6], Seeliger C[7,8], Nussler AK[9], Ehnert S[10].
Author information

Abstract

Human adipose mesenchymal stem/stromal cells (Ad-MSCs) have been proposed as a suitable option for bone tissue engineering. However, donor age, weight, and gender might affect the outcome. There is still a lack of knowledge of the effects the donor tissue site might have on Ad-MSCs function. Thus, this study investigated proliferation, stem cell, and osteogenic differentiation capacity of human Ad-MSCs obtained from subcutaneous fat tissue acquired from different locations (abdomen, hip, thigh,

knee, and limb). Ad-MSCs from limb and knee showed strong proliferation despite the presence of osteogenic stimuli, resulting in limited osteogenic characteristics. The less proliferative Ad-MSCs from hip and thigh showed the highest alkaline phosphatase (AP) activity and matrix mineralization. Ad-MSCs from the abdomen showed good proliferation and osteogenic characteristics. Interestingly, the observed differences were not dependent on donor age, weight, or gender, but correlated with the expression of *Sox2*, *Lin28A*, *Oct4α*, and *Nanog*. Especially, low basal *Sox2* levels seemed to be pivotal for osteogenic differentiation. Our data clearly show that the donor tissue site affects the proliferation and osteogenic differentiation of Ad-MSCs significantly. Thus, for bone tissue engineering, the donor site of the adipose tissue from which the Ad-MSCs are derived should be adapted depending on the requirements, e.g., cell number and differentiation state.

J Cell Physiol. 2018 Jun 26. doi: 10.1002/jcp.26860. [Epub ahead of print]

Fibroblasts and mesenchymal stem cells: Two sides of the same coin?

Soundararajan M[1], Kannan S[2].
Author information

Abstract

Mesenchymal stem/stromal cells (MSCs) have gained considerable popularity owing to the vast possibilities and lack of ethical constraints and risks normally associated with other stem cells, such as embryonic stem cells. However, they are morphologically indistinguishable from fibroblasts. This review aims to assess the similarities and differences between the two cell types, and the possible relationship between them. We found that the two cells seem almost identical with respect to their surface immunophenotype, proliferation, and differentiation capacities and even, to an extent, their gene expression profiles and immunomodulatory capacities. There are some differences in capability between the two cells, with MSCs being more efficient than fibroblasts. Even so, the similarities are so striking, that, if we were to follow the current criteria provided by the International Society for Cellular Therapy, fibroblasts ought to be named as MSCs. One promising marker is their DNA methylation profiles. Nonetheless, without any other marker to differentiate between the cells in the first place, it would be difficult to find a definitive marker. Interestingly, the differences observed between the two cells have also been observed between young and old MSCs. This also seems to be true of certain cell surface markers. Therefore, it is possible that fibroblasts are in fact aged MSCs and that the two cells are the same.

Histol Histopathol. 2018 Jul 3:18018. doi: 10.14670/HH-18-018. [Epub ahead of print]

PRP and MSCs on tenocytes artificial wound healing: an in vitro study comparing fresh and frozen PRP.

Veronesi F[1], Pagani S[2], Torricelli P[1], Filardo G[3], Cavallo C[4], Grigolo B[4], Fini M[1].
Author information

Abstract

Evolutionary medicine has proven helpful to understand the origin of human disease, e.g. in identifying causal roles of recent environmental changes impacting on human physiology (environment-phenotype mismatch). In contrast, diseases affecting only a limited number of members of a species often originate from evolutionary trade-offs for usually physiologic adaptations assuring reproductive success in the context of extrinsic threats. For example, the G1 and G2 variants of the APOL1 gene supporting control of Trypanosoma infection come with the trade-off that they promote the progression of kidney disease. In this review we extend the concept of evolutionary nephrology by discussing how the physiologic adaptations (danger responses) to tissue injury create evolutionary trade-offs that drive histopathological changes underlying acute and chronic kidney diseases. The evolution of multicellular organisms positively selected a number of danger response programs for their overwhelming benefits in assuring survival such as clotting, inflammation, epithelial healing and mesenchymal healing, i.e. fibrosis and sclerosis. Upon kidney injury these danger programs often present as pathomechanisms driving persistent nephron loss and renal failure. We explore how classic kidney disease entities involve insufficient or overshooting activation of these danger response programs for which the underlying genetic basis remains largely to be defined. Dissecting the causative and hierarchical relationships between danger programs should help to identify molecular targets to control kidney injury and to improve disease outcomes.Tendon tissue has poor regenerative capacity due to its low vascularization, cell density and extracellular matrix (ECM) production. Therefore, tendon injuries are an increasing clinical problem because of the formation of scar tissue with traditional therapies. Regenerative medicine aims at triggering a healing response through the use of biological treatments such as mesenchymal stromal cells (MSCs) and growth factors (GFs). MSCs show several advantages in tendon clinical setting, while platelet rich plasma (PRP) has gained popularity because of its high GF concentration, although its applications in the tendon clinical setting are still controversial. The aim of the present study was to evaluate a combined treatment of MSCs and PRP in an in vitro microwound model of tendon injuries. In addition, fresh and frozen PRP were compared. Single human tenocytes cultures or co-cultures with bone marrow derived MSCs (BMSCs) were set up with or without human PRP, fresh or frozen. After 24 hours of culture, it was observed that MSCs alone significantly increased tenocyte migration speed, microwound healing rate, fibronectin, collagen I and aggrecan production. These effects were enhanced by the combination with PRP, fresh being more effective than frozen PRP. In addition, the number of MSCs and tenocytes inside the microwound was significantly increased, especially with fresh PRP. In conclusion, the combination of MSCs and PRP, especially the fresh one, increases tenocytes and MSC migration speed, as well as ECM protein production compared to the use of MSCs alone.

BMB Rep. 2018 Jul 3. pii: 4198. [Epub ahead of print]

Exosomes Derived from MicroRNA-584 Transfected Mesenchymal Stem Cells: Novel Alternative Therapeutic Vehicles for Cancer Therapy.

Kim R[1], Lee S[1], Lee J[1], Kim M[1], Kim WJ[1], Lee HW[1], Lee MY[2], Kim J[3], Chang W[1].
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Abstract

Exosomes are small membranous vesicles which contain abundant RNA molecules, and are transferred from releasing cells to uptaking cells. MicroRNA (miRNA) is one of the transferred molecules affecting the adopted cells, including glioma cells. We hypothesized that mesenchymal stem cells (MSCs) can secrete exosomes loading miRNA and have important effects on the progress of gliomas. To determine these effects by treating exosomal miRNA in culture media of miRNA mimic transfected MSCs, we assessed the in vitro cell proliferation and invasion capabilities, and the expression level of relative proteins associated with cell apoptosis, growth and migration. For animal studies, the mice injected with U87 cells were exposed to exosomes derived from miRNA-584-5p transfected MSCs, to confirm the influence of exosomal miRNA on the progress of glioma. Based on our results, we propose a new targeted cancer therapy wherein exosomes derived from miRNA transfected MSCs could be used to modulate tumor progress as the anticancer vehicles.

Cancer Gene Ther. 2018 Jun 29. doi: 10.1038/s41417-018-0034-1. [Epub ahead of print]

Inducible Caspase9-mediated suicide gene for MSC-based cancer gene therapy.

Rossignoli F[1], Grisendi G[2,3], Spano C[2,3], Golinelli G[2], Recchia A[4], Rovesti G[2], Orsi G[2], Veronesi E[2,5], Horwitz EM[6], Dominici M[7,8].
Author information
Abstract

Cellular therapies based on mesenchymal stromal/stem cells (MSC) are promising strategies in regenerative medicine and oncology. Despite encouraging results, there is still some level of concerns on inoculating MSC in cancer patients. To face this issue, one possibility resides in engineering MSC by incorporating a suicide gene in order to control their fate once infused. Strategies based on Herpes Simplex Virus Thymidine Kinase (HSV-TK) and the Cytosine Deaminase genes have been developed and more recently a novel suicide gene, namely, iCasp9, has been proposed. This approach is based on a variant of human Caspase9 that binds with high affinity to a synthetic, bioinert small molecule (AP20187) leading to cell death. Based on this technology so far marginally applied to MSC, we tested the suitability of iCasp9 suicide strategy in MSC to further increase their safety. MSC have been transfected by a lentiviral vector carrying iCasp9 gene and then tested for viability after AP20187 treatment in comparison with mock-transfected cells. Moreover, accounting our anti-tumor approaches based on MSC expressing potent anti-cancer ligand TNF-Related Apoptosis-Inducing Ligand (TRAIL), we generated adipose MSC co-expressing iCasp9 and TRAIL successfully targeting an aggressive sarcoma type. These data show that anti-cancer and suicide mechanisms can coexist without affecting cells performance and hampering the tumoricidal activity mediated by TRAIL. In conclusion, this study originally indicates the suitability of combining a MSC-based anti-cancer gene approach with iCasp9 demonstrating efficiency and specificity.