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Transforming Growth Factor-β Promotes Homing and Therapeutic Efficacy of Human Mesenchymal Stem Cells to Glioblastoma.

Li M[1], Zeng L[2], Liu S[2], Dangelmajer S[3], Kahlert UD[4], Huang H[5], Han Y[2], Chi X[1], Zhu M[2,6], Lei T[1,2].
Author information

Abstract

Human mesenchymal stem cell-based tumor therapeutic gene delivery is regarded as a promising strategy for the treatment of glioblastoma (GBM). However, the efficiency of these stem cells to home to the target sites limits their potential curative effect and clinical application. In this work, we provide a novel pretreatment approach for enhancing the homing capacity of human adipose-derived mesenchymal stem cells(hAMSCs) for stem cell-based tumor gene delivery for GBM therapy. Pre-exposure of these stem cells to TGF-β resulted in enhanced homing ability to GBM through increasing CXC chemokine receptor 4 (CXCR4) expression, as evidenced by a diminishing homing capacity when inhibition of the TGF-β receptor II and CXCR4 was applied. In addition, by pretreating hAMSCs expression of tumor necrosis factor-related apoptosis-inducing ligand with TGF-β, we achieved significant enhancements in the therapeutic efficacy as demonstrated by an increased number of migrated hAMSCs to target sites, decreased tumor volume, and prolonged survival time in a murine model of GBM. These findings highlight a straightforward method in which cell preconditioning methodology is utilized to promote therapeutic efficacy of a biological treatment for GBM.

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Exploiting tumor-intrinsic signals to induce mesenchymal stem cell-mediated suicide gene therapy to fight malignant glioma.

Li M[1,2], Sun S[3], Dangelmajer S[4], Zhang Q[5], Wang J[5], Hu F[5], Dong F[5], Kahlert UD[6], Zhu M[7], Lei T[5].

Author information

Abstract

BACKGROUND:

Human mesenchymal stem cell (MSC)-based tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) gene delivery is regarded as an effective treatment for glioblastoma (GBM). However, adverse-free target site homing of the delivery vehicles to the tumor microsatellite nests is challenging, leading to erroneously sustained released of this suicide protein into the normal brain parenchyma; therefore, limiting off-target cytotoxicity and controlled expression of the suicide inductor is a prerequisite for the safe use of therapeutic stem cells.

METHODS:

Utilizing the intrinsic expression profile of GBM and its elevated expression of TGF-β relative to normal brain tissue, we sought to engineer human adipose-derived MSCs (hAMSC-SBE4-TRAIL) which augment the expression of TRAIL under the trigger of TGF-β signaling. We validated our therapeutic technology in a series of functional in vitro and in vivo assays using primary patient-derived GBM models.

RESULTS:

Our current findings show that these biologic delivery vehicles have high tumor tropism efficacy and expression TRAIL gene under the trigger of TGF-β-secreting GBMs, as well as avoid unspecific TRAIL secretion into normal brain tissue. hAMSC-SBE4-TRAIL inhibited the proliferation and induced apoptosis in experimental GBMs both in vitro and in vivo. In addition, our improved platform of engineered MSCs significantly decreased the tumor volume and prolonged survival time in a murine model of GBM.

CONCLUSIONS:

Our results on the controlled release of suicide inductor TRAIL by exploiting an endogenous tumor signaling pathway demonstrate a significant improvement for the clinical utility of stem cell-mediated gene delivery to treat brain cancers. Harvesting immune-compatible MSCs from patients' fat by minimally invasive procedures further highlights the clinical potential of this approach in the vision of applicability in a personalized manner. The hAMSC-SBE4-TRAIL exhibit great curative efficacy and are a promising cell-based treatment option for GBM to be validated in clinical exploration.

Clin Transl Med. 2019 Mar 15;8(1):8. doi: 10.1186/s40169-019-0224-y.

Cell membrane protein functionalization of nanoparticles as a new tumor-targeting strategy.

Pasto A[1,2], Giordano F[3,2], Evangelopoulos M[2], Amadori A[1,4], Tasciotti E[5,6].
Author information

Abstract

Nanoparticles have seen considerable popularity as effective tools for drug delivery. However, non-specific targeting continues to remain a challenge. Recently, biomimetic nanoparticles have emerged as an innovative solution that exploits biologically-derived components to improve therapeutic potential. Specifically, cell membrane proteins extracted from various cells (i.e., leukocytes, erythrocytes, platelets, mesenchymal stem cells, cancer) have shown considerable promise in bestowing nanoparticles with increased circulation and targeting efficacy. Traditional nanoparticles can be detected and removed by the immune system which significantly hinders their clinical success. Biomimicry has been proposed as a promising approach to overcome these limitations. In this review, we highlight the current trends in biomimetic nanoparticles and describe how they are being used to increase their chemotherapeutic effect in cancer treatment.

Sci Rep. 2019 Mar 14;9(1):4468. doi: 10.1038/s41598-019-41100-9.

Stem cell-derived extracellular vesicles inhibit and revert fibrosis progression in a mouse model of diabetic nephropathy.

Grange C[1,2], Tritta S[2], Tapparo M[1], Cedrino M[2], Tetta C[3], Camussi G[4,5,6], Brizzi MF[7,8,9].
Author information

Abstract

Extracellular vesicles (EVs) that are derived from mesenchymal stromal cells (MSCs) have been shown to reprogram injured cells by activating regenerative processes. We herein investigate the potential therapeutic effect of EVs, shed by human bone marrow MSCs and by human liver stem-like cells (HLSCs), on the progression and reversion of fibrosis in a mouse model of diabetic nephropathy, as induced by streptozotocin. After the development of nephropathy, stem cell-derived EVs were administered weekly to diabetic mice for four weeks. The stem cell-derived EV treatment, but not the fibroblast EV treatment that was used as a control, significantly ameliorated functional parameters, such as albumin/creatinine excretion, plasma creatinine and blood urea nitrogen, which are altered in diabetic mice. Moreover, the renal fibrosis that develops during diabetic nephropathy progression was significantly inhibited in stem cell EV-treated animals. A correlation was found between the down regulation of several pro-fibrotic genes in renal tissues and the anti-fibrotic effect of HLSC and MSC EVs. A comparative analysis of HLSC and MSC EV miRNA content highlighted some common and some specific patterns of miRNAs that target predicted pro-fibrotic genes. In conclusion, stem cell-derived EVs inhibit fibrosis and prevent its progression in a model of diabetes-induced chronic kidney injury.