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Metformin impairs homing ability and efficacy of mesenchymal stem cells for cardiac repair in streptozotocin-induced diabetic cardiomyopathy in rats

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Abstract

Bone marrow derived mesenchymal stem cells (BM-MSCs) have demonstrated potential in treating diabetic cardiomyopathy. However, diabetic patients are on multiple drugs and there is lack of understanding on how transplanted stem cells would respond in presence of such drugs. Metformin is an AMP Kinase (AMPK) activator, the widest used anti-diabetic drug. In this study, we investigated the effect of metformin on the efficacy of stem cell therapy in a diabetic cardiomyopathy animal model using streptozotocin (STZ) in male Wistar rats. To comprehend the effect of metformin on the efficacy of BM-MSCs, we transplanted BM-MSCs (1 million cells/rat) with or without metformin. Our data demonstrate that transplantation of BM-MSCs prevented cardiac fibrosis and promoted angiogenesis in diabetic hearts. However, metformin supplementation downregulated BM-MSCs mediated cardioprotection. Interestingly, both BM-MSCs and metformin treatment individually, improved cardiac function with no synergistic effect of metformin supplementation along with BM-MSCs. Investigating the mechanisms of loss of efficacy of BM-MSCs in the presence of metformin, we found that metformin treatment impairs

homing of implanted BM-MSCs in the heart and leads to poor survival of transplanted cells. Furthermore, our data demonstrate that metformin mediated activation of AMPK is responsible for poor homing and survival of BM-MSCs in the diabetic heart. Hence, current study confirms that a conflict arises between metformin and BM-MSCs for treating diabetic cardiomyopathy. Approximately 10% of the world population is diabetic to which metformin is prescribed very commonly. Hence, future cell replacement therapies in combination with AMPK inhibitors may be more effective for diabetic patients.

Cancer Res

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Mesenchymal stem cell-secreted extracellular vesicles instruct stepwise dedifferentiation of breast cancer cells into dormancy at the bone marrow perivascular region

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Abstract

In the bone marrow (BM), breast cancer (BC) cells (BCC) can survive in dormancy for decades as cancer stem cells (CSC), resurging as tertiary metastasis. The endosteal region where BCCs exist as CSCs poses a challenge to target them, mostly due to the co-existence of endogenous hematopoietic stem cells. This study addresses the early period of dormancy when BCCs enter BM at the perivascular region to begin the transition into CSCs, which we propose as the final step in dormancy. A two-step process comprises the Wnt-β-catenin pathway mediating BCC dedifferentiation into CSCs at the BM perivascular niche.

At this site, BCCs responded to two types of mesenchymal stem cell (MSC)-released extracellular vesicles (EV) that may include exosomes. Early released EVs began the transition into cycling quiescence, DNA repair, and reorganization into distinct BCC subsets. After contact with BC, the content of EVs changed (primed) to complete dedifferentiation into a more homogeneous population with CSC properties. BCC progenitors (Oct4alo), which are distant from CSCs in a hierarchical stratification, were sensitive to MSC EVs. Despite of CSC function, Oct4alo BCCs expressed multipotent pathways similar to CSCs. Oct4alo BCCs dedifferentiated and co-localized with MSCs (murine and human BM) in vivo. Overall, these findings elucidate a mechanism of early dormancy at the BM perivascular region and provide evidence of epigenome reorganization as a potential new therapy for BC.

Cytotherapy

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Pre-clinical investigation of mesenchymal stromal cell-derived extracellular vesicles: a systematic review

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Abstract

The therapeutic potential of naturally secreted micro- and nanoscale extracellular vesicles (EVs) makes them attractive candidates for regenerative medicine and pharmaceutical science applications. To date, the results of numerous publications have shown the practicality of using EVs to replace mesenchymal stromal cells (MSCs) or liposomes. This article presents a systematic review of pre-clinical studies conducted over the past decade of MSC-derived EVs (MSC-EVs) used in animal models of disease. The authors searched the

relevant literature in the PubMed and Scopus databases (9358 articles), and 690 articles met the inclusion criteria. The eligible articles were placed in the following disease categories: autoimmune, brain, cancer, eye, gastrointestinal, heart, inflammation/transplantation, liver, musculoskeletal, pancreas, spinal cord and peripheral nervous system, respiratory system, reproductive system, skin, urinary system and vascular-related diseases. Next, the eligible articles were assessed for the rate of publication and global distribution, methodology of EV isolation and characterization, route of MSC-EV administration, length of follow-up, source of MSCs and animal species. The current review classifies and critically discusses the technical aspects of these MSC-EV animal studies and discusses potential relationships between methodological details and the effectiveness of MSC-EVs as reported by these pre-clinical studies.

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Recent advances in drug delivery systems for targeting cancer stem cells

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Free PMC article

Abstract

Cancer stem cells (CSCs) are a subpopulation of cancer cells with functions similar to those of normal stem cells. Although few in number, they are capable of self-renewal, unlimited proliferation, and multi-directional differentiation potential. In addition, CSCs have the ability to escape immune surveillance. Thus, they play an important role in the occurrence and development of tumors, and they are closely related to tumor invasion, metastasis,

drug resistance, and recurrence after treatment. Therefore, specific targeting of CSCs may improve the efficiency of cancer therapy. A series of corresponding promising therapeutic strategies based on CSC targeting, such as the targeting of CSC niche, CSC signaling pathways, and CSC mitochondria, are currently under development. Given the rapid progression in this field and nanotechnology, drug delivery systems (DDSs) for CSC targeting are increasingly being developed. In this review, we summarize the advances in CSC-targeted DDSs. Furthermore, we highlight the latest developmental trends through the main line of CSC occurrence and development process; some considerations about the rationale, advantages, and limitations of different DDSs for CSC-targeted therapies were discussed.

Keywords: ABC, ATP binding cassette; AFN, apoferritin; ALDH, aldehyde dehydrogenase; BM-MSCs-derived Exos, bone marrow mesenchymal stem cells-derived exosomes; Biomarker; CAFs, cancer-associated fibroblasts; CL-siSOX2, cationic lipoplex of SOX2 small interfering RNA; CMP, carbonate-mannose modified PEI; CQ, chloroquine; CSCs, cancer stem cells; Cancer stem cells; Cancer treatment; Cellular level; DCLK1, doublecortin-like kinase 1; DDSs, drug delivery systems; DLE, drug loading efficiency; DOX, doxorubicin; DQA-PEG2000-DSPE, dequlinium and carboxyl polyethylene glycol-distearoylphosphatidylethanolamine; Dex, dexamethasone; Drug delivery systems; ECM, extracellular matrix; EMT, epithelial–mesenchymal transition; EPND, nanodiamond-Epirubicin drug complex; EpCAM, epithelial cell adhesion molecule; GEMP, gemcitabine monophosphate; GLUT1, glucose ligand to the glucose transporter 1; Glu, glucose; HCC, hepatocellular carcinoma; HH, Hedgehog; HIF1α, hypoxia-inducible factor 1-alpha; HNSCC, head and neck squamous cell carcinoma; IONP, iron oxide nanoparticle; LAC, lung adenocarcinoma; LNCs, lipid nanocapsules; MAPK, mitogen-activated protein kinase; MB, methylene blue; MDR, multidrug resistance; MNP, micellar nanoparticle; MSNs, mesoporous silica nanoparticles; Molecular level; NF-κB, nuclear factor-kappa B; Nav, navitoclax; Niche; PBAEs, poly(β-aminoester); PDT, photodynamic therapy; PEG-PCD, poly(ethylene glycol)-block-poly(2-methyl-2-carboxyl-propylene carbonate-graft-dodecanol); PEG-PLA, poly(ethylene glycol)-b-poly(d,l-lactide); PEG-b-PLA, poly(ethylene glycol)-block-poly(d,l-lactide); PLGA, poly(ethylene glycol)-poly(d,l-lactide-co-glycolide); PTX, paclitaxel; PU-PEI, polyurethane-short branch-polyethylenimine; SLNs, solid lipid nanoparticles; SSCs, somatic stem cells; Sali-ABA, 4-(aminomethyl) benzaldehyde-modified Sali; TNBC, triple negative breast cancer; TPZ, tirapazamine; Targeting strategies; cRGD, cyclic Arg-Gly-Asp; iTEP, immune-tolerant, elastin-like polypeptide; mAbs, monoclonal antibodies; mPEG-b-PCC-g-GEM-g-DC-g-CAT, poly(ethylene glycol)-block-poly(2-methyl-2-carboxyl-propylenecarbonate-graft-dodecanol-graft-cationic ligands); ncRNA, non-coding RNAs; uPAR, urokinase plasminogen activator receptor.