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Impedance-Based Monitoring of Mesenchymal Stromal Cell Three-Dimensional Proliferation Using Aerosol Jet Printed Sensors: A Tissue Engineering Application.

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Abstract

One of the main hurdles to improving scaffolds for regenerative medicine is the development of non-invasive methods to monitor cell proliferation within three-dimensional environments. Recently, an electrical impedance-based approach has been identified as promising for three-dimensional proliferation assays. A low-cost impedance-based solution, easily integrable with multi-well plates, is here presented. Sensors were developed using biocompatible carbon-based ink on foldable polyimide substrates by means of a novel aerosol jet printing technique. The setup was tested to monitor the proliferation of human mesenchymal stromal cells into previously validated gelatin-chitosan hybrid hydrogel scaffolds. Reliability of the methodology was assessed comparing variations of the electrical impedance parameters with the outcomes of enzymatic proliferation assay. Results obtained showed a magnitude increase and a phase angle decrease at 4 kHz (maximum of 2.5 kΩ and -9 degrees) and an exponential increase of the modeled resistance and capacitance components due to the cell proliferation (maximum of 1.5 kΩ and 200 nF). A statistically significant relationship with enzymatic assay outcomes could be detected for both phase angle and electric model parameters. Overall, these findings support the potentiality of this non-invasive approach for continuous monitoring of scaffold-based cultures, being also promising in the perspective of optimizing the scaffold-culture system.

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Adipose mesenchymal stromal/stem cells expanded by a GMP compatible protocol displayed improved adhesion on cancer cells in flow conditions.

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Abstract

BACKGROUND:

Adipose tissue derived mesenchymal stromal/stem cells (ASC) can be expanded using supernatant rich in growth factors (SRGF) as Good Manufacturing Practice compatible additive, instead of fetal bovine serum (FBS). After transendothelial migration, ASC can migrate to cancer masses where they can release active substances. Due to their homing and secretion properties ASC can be used as targeted

drug delivery vehicles. Nevertheless, the fraction of ASC actually reaching the tumor target is limited. The impact of culture conditions on ASC homing potential on cancer cells is unknown.

METHODS:

In dynamic *in vitro* conditions, we perfused FBS or SRGF ASC in flow chambers coated with collagen type I and fibronectin or seeded with endothelial cells or with HT1080, T98G and Huh7 cancer cells. Expression of selected adhesion molecules was evaluated by standard cytofluorimetry. Dynamic intracellular calcium concentration changes were evaluated in microfluidic and static conditions.

RESULTS:

When compared to FBS ASC, not specific adhesion of SRGF ASC on collagen type I and fibronectin was lower (-33.9%±12.2% and -45.3%±16.9%), while on-target binding on HT1080 and T98G was enhanced (+147%±8% and 120.5%±5.2%). Adhesion of both FBS and SRGF ASC on Huh7 cells was negligible. As confirmed by citofluorimetry and by function-blocking antibody, SRGF mediated decrease of CD49a expression accounted for lower SRGF-ASC avidity for matrix proteins. Upon stimulation with calcium ionophore in static conditions, mobilization of intracellular calcium in SRGF ASC was greater than in FBS ASC. In dynamic conditions, upon adhesion on matrix proteins and HT1080 cells, SRGF ASC showed marked oscillatory calcium concentration changes.

CONCLUSIONS:

SRGF can enhance specific ASC binding capacity on selected cancer cells as HT1080 (fibrosarcoma) and T98G (glioblastoma) cells. Upon cell-cell adhesion, SRGF ASC activate intracellular responses potentially improving cell secretion functions. SRGF ASC could be considered as suitable drug delivery vehicle for cancer therapy.

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Activation PDGFR-α/AKT Mediated Signaling Pathways in Oral Squamous Cell Carcinoma by Mesenchymal Stem/Stromal Cells Promotes Anti-apoptosis and Decreased Sensitivity to Cisplatin.

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Abstract

Desmoplasia, a hallmark of a head and neck cancer, has both biologic and physiologic effects on cancer progression and chemotherapeutic response. Mesenchymal stem/stromal cells (MSCs), also known as mesenchymal stromal progenitor cells, have been shown to play a role in cancer progression, alter apoptotic responses, and confer resistance to chemotherapy in various carcinomas. The pathophysiology of MSCs with respect to tumorigenesis is widely reported in other cancers and is sparsely reported in oral squamous cell carcinomas (OSCCs). We previously reported paracrine mediated PDGF-AA/PDGFR-α signaling to underlie MSCs chemotaxis in OSCC. Given the poor clinical response to primary chemotherapy, we hypothesized that MSCs may alter cancer cell sensitivity to

cisplatin through activation of PDGFR-α mediated signaling pathways. Co-culture of MSCs with human derived OSCC cell lines, JHU-012 and -019, resulted in a significant increase in the production of PDGF-AA and MCP-1 compared to cancer cells grown alone ($p < 0.005$) and was accompanied by an increase in the phosphorylation state of PDGFR-α ($p < 0.02$) and downstream target AKT at S473 ($p < 0.025$) and T308 ($p < 0.02$). JHU-012 and -019 cancer cells grown in co-culture were significantly less apoptotic ($p < 0.001$), expressed significantly higher levels of Bcl-2 ($p < 0.04$) with a concomitant significant decrease in bid expression ($p < 0.001$) compared to cancer cells grown alone. There was a significant increase in the cisplatin dose response curve in cancer cell clones derived from JHU-012 and 019 cancer cells grown in co-culture with MSCs compared to clones derived from cancer cells grown alone ($p < 0.001$). Moreover clones derived from JHU-012 cells grown in co-culture with MSCs were significantly more susceptible to cisplatin following pretreatment with, crenolanib, a PDGFR inhibitor, compared to cancer cells grown alone or in co-culture with MSCs ($p < 0.0001$). These findings suggest that crosstalk between cancer cells and MSCs is mediated, at least in part, by activation of autocrine PDGF-AA/PDGFR-α loop driving AKT-mediated signaling pathways, resulting in reduced cancer cell sensitivity to cisplatin through alterations in apoptosis.

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Mesenchymal Stem Cells Engineered by Modified Polyethylenimine Polymer for Targeted Cancer Gene Therapy, in Vitro and in Vivo

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Abstract

Cell-based delivery system is a promising strategy to protect therapeutic agents from the immune system and provide targeted delivery. Mesenchymal stem cells (MSCs) have recently been introduced as an encouraging vehicle in cell-based gene therapy due to their unique features including tumor-tropic property and migratory ability. However, gene

transfer into MSCs is limited due to low efficiency and cytotoxicity of carriers. In this study, we designed a novel delivery system based on polyethylenimine (PEI_{25}) to improve these features of carrier and transfect plasmid encoding TRAIL to MSCs. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a death ligand of TNF family with selective effect on cancerous cells. Then, death induction and migration ability of TRAIL-expressing MSCs was studied in melanoma cells. The effect of engineered-MSCs as an anti-tumor vehicle was also investigated in mice bearing melanoma cells. Our findings indicated that heterocyclic amine derivative of PEI_{25} showed significant improvement in MSCs viability determined by MTT assay and gene expression using fluorescent microscopy, flow cytometry and Western blot analysis. We observed that engineered-MSCs could migrate toward and induce cell death in B16F0 cells in vitro. The single administration of TRAIL-expressing MSCs could delay tumor appearance and efficiently reduce tumor weights. Hematoxylin and eosin staining of tumor sections revealed extensive neoplastic cells necrosis. Furthermore, engineered-MSCs could migrate and localize to tumors sites within five days. Our results indicated that MSCs engineered by modified-PEI/TRAIL complexes could be considered as a promising cellular vehicle for targeted tumor suppression.

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3D-bioprinted Functional and Biomimetic Hydrogel Scaffolds Incorporated With Nanosilicates to Promote Bone Healing in Rat Calvarial Defect Model

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Abstract

Three-dimensional (3D) bioprinting is an extremely convenient biofabrication technique for creating biomimetic tissue-engineered bone constructs and has promising applications in regenerative medicine. However, existing bioinks have shown low mechanical strength, poor osteoinductive ability, and lacking a suitable microenvironment for laden cells. Nanosilicate (nSi) has shown to be a promising biomaterial, due to its unique properties such as excellent biocompatibility, degrade into nontoxic products, and with osteoinductive properties, which has been used in bone bioprinting. However, the long term bone healing effects and associating risks, if any, of using nSi in tissue engineering bone scaffolds in vivo are unclear and require a more thorough assessment prior to practical use. Hence, a functional and biomimetic nanocomposite bioink composed of rat bone marrow mesenchymal stem cells (rBMSCs), nSi, gelatin and alginate for the 3D bioprinting of tissue-engineered bone constructs is firstly demonstrated, mimicking the structure of extracellular matrix, to create a conducive microenvironment for encapsulated cells. It is shown that the addition of nSi significantly increases the printability and mechanical strength of fabricated human-scale tissue or organ structures (up to 15 mm height) and induces osteogenic differentiation of the encapsulated rBMSCs in the absence of in vitro osteoinductive factors. A systematic in vivo research of the biomimetic nanocomposite bioink scaffolds is further demonstrated in a rat critical-size (8 mm) bone defect-repair model. The in vivo results demonstrate that the 3D bioprinted nanocomposite scaffolds can significantly promote the bone healing of the rat calvarial defects compared to other scaffolds without nSi or cells, and show rarely side effects on the recipients. Given the above advantageous properties, the 3D bioprinted nanocomposite scaffolds can greatly accelerate the bone healing in critical bone defects, thus providing a clinical potential candidate for orthopedic applications.