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The history of bone marrow in orthopaedic surgery (part I trauma): trepanning, bone marrow injection in damage control resuscitation, and bone marrow aspiration to heal fractures.

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Abstract

PURPOSE:

One of the oldest procedures performed by man is trepanning of the bone and yet it was only in the last 40 years that bone marrow aspiration has been used to treat nonunion disorders.

MATERIAL AND METHODS:

These advances were possible due to improvements in instruments and in techniques to make holes in the bone, an history that began with skull trephinations around 8000-10,000 years ago, and continued with sternum bone marrow injection for trauma resuscitation in the beginning of the twentieth century; this procedure had improved at the beginning of the twenty-first century to allow pelvis bone marrow aspiration for the treatment of nonunion.

RESULTS:

Trephined skulls from antiquity have been found in many parts of world, showing that trephining was ancient and widespread. Beginning with Neolithic period and the pre-Columbian Andean civilizations, the authors have traced the development of this surgical skill by describing the various surgical tools used to perform holes in the skull. These tools (trephines or trepan) were proposed at the end of the nineteenth century to study the bone marrow. At the beginning of the twentieth century, the sternum became the center of interest for the "in vivo" study of the bone marrow and the fluid injection in the sternum's bone marrow was described for resuscitation from shock during the World War II. With the introduction of plastic catheters and improved cannulation techniques, the need for intraosseous infusion as an alternative route for intravenous access diminished and sometimes abandoned. However, during the mid-1980s, James Orlowski allowed renaissance of the use of intraosseous infusion for paediatric resuscitation. Since then, this technique has become widespread and is now recognized as an alternative to intravenous access in adult emergencies; particularly, the intraosseous access has received class IIA recommendation from the Advanced Trauma Life Support program supported by the American College of Surgeons Committee on Trauma and bone marrow infusion is now recommended for "Damage Control" resuscitation. Although the pelvis bone contains half of the body's marrow volume, it was only in 1950 that the pelvis was proposed as a source for bone marrow aspiration and bone marrow-derived mesenchymal stem cells to improve healing of fractures.

CONCLUSION:

It will be many years before doing holes in the bone as orthopaedic trauma procedure will be relegated to the annals of history.

Biofabrication. 2020 Feb 12. doi: 10.1088/1758-5090/ab7553. [Epub ahead of print]

Engineering considerations on extrusion-based bioprinting: interactions of material behaviour, mechanical forces and cells in the printing needle.

Emmermacher J[1], Spura D[2], Cziommer J[3], Kilian D[4], Wollborn T[5], Fritsching U[6], Steingroewer J[7], Walther T[8], Gelinsky M[9], Lode A[10].

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Abstract

Systematic analysis of the extrusion process in 3D bioprinting is mandatory for process optimization concerning production speed, shape fidelity of the 3D construct and cell viability. In this study, we applied numerical and analytical modelling to describe the fluid flow inside the printing head based on a Herschel-Bulkley model. The presented analytical calculation method nicely reproduces the results of Computational Fluid Dynamics (CFD) simulation concerning pressure drop over the printing head and maximal shear parameters at the outlet. An approach with dimensionless flow parameter enables the user to adapt rheological characteristics of a bioink, the printing pressure and needle diameter with regard to processing time, shear sensitivity of the integrated cells, shape fidelity and strand dimension. Bioinks consist of a blend of polymers and cells, which lead to a complex fluid behavior. In the present study, a bioink containing alginate, methylcellulose and agarose (AMA) was used as experimental model to compare the calculated with the experimental pressure gradient. With cultures of an immortalized human mesenchymal stem cell line and plant cells (basil) it was tested how cells influence the flow and how mechanical forces inside the printing needle affect cell viability. Influences on both sides increased with cell (aggregation) size as well as a less spherical shape. This study contributes to a systematic description of the extrusion-based bioprinting process and introduces a general strategy for process design, transferable to other bioinks.

Molecules. 2020 Feb 7;25(3). pii: E715. doi: 10.3390/molecules25030715.

Cell-Based Nanoparticles Delivery Systems for Targeted Cancer Therapy: Lessons from Anti-Angiogenesis Treatments.

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Abstract

The main strategy of cancer treatment has focused on attacking the tumor cells. Some cancers initially responsive to chemotherapy become treatment-resistant. Another strategy is to block the formation of tumor vessels. However, tumors also become resistant to anti-angiogenic treatments, mostly due to other cells and factors present in the tumor microenvironment, and hypoxia in the central part of the tumor. The need for new cancer therapies is significant. The use of nanoparticle-based therapy will improve therapeutic efficacy and targeting, while reducing toxicity. However, due to inefficient accumulation in tumor sites, clearance by reticuloendothelial organs and toxicity, internalization or conjugation of drug-loaded nanoparticles (NPs) into mesenchymal stem cells (MSCs) can increase efficacy by actively delivering them into the tumor microenvironment. Nanoengineering MSCs with drug-loaded NPs can increase the drug payload delivered to tumor sites due to the migratory and homing abilities of MSCs. However, MSCs have some disadvantages, and exosomes and membranes from different cell types can be used to transport drug-loaded NPs actively to tumors. This review gives an overview of different cancer approaches, with a focus on hypoxia and the emergence of NPs as drug-delivery systems and MSCs as cellular vehicles for targeted delivery due to their tumor-homing potential.

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Mesenchymal stem cells as carriers for systemic delivery of oncolytic viruses.

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Abstract

Progress in genetic engineering led to the emergence of some viruses as potent anticancer therapeutics. These oncolytic viruses combine self-amplification with dual antitumor action: oncolytic (destruction of cancer cells) and immunostimulatory (eliciting acquired antitumor response against cancer epitopes). As any other viruses, they trigger antiviral response upon systemic administration. Mesenchymal stem cells are immature cells capable of self-renewing and differentiating into many cell types that belong to three germinal layers. Due to their inherent tumor tropism mesenchymal stem cells loaded with oncolytic virus can improve delivery of the therapeutic cargo to cancer sites. Shielding of oncolytic viral construct from antiviral host immune response makes these cells prospective delivery vehicles to even hard-to-reach metastatic neoplastic foci. Use of mesenchymal stem cells has been criticized by some investigators as limiting proliferative abilities of primary cells and increasing the risk of malignant transformation, as well as attenuating therapeutic responses. However, majority of preclinical studies indicate safety and efficacy of mesenchymal stem cells used as carriers of oncolytic viruses. In view of contradictory postulates, the debate continues. The review discusses mesenchymal stem cells as carriers for delivery of genetically engineered oncolytic constructs and focuses on systemic approach to oncoviral treatment of some deadly neoplasms.

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Mesenchymal Stem Cells in the Tumor Microenvironment.

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Abstract

The interactions between tumor cells and the non-malignant stromal and immune cells that make up the tumor microenvironment (TME) are critical to the pathophysiology of cancer. Mesenchymal stem cells (MSCs) are multipotent stromal stem cells found within most cancers and play a critical role influencing the formation and function of the TME. MSCs have been reported to support tumor growth through a variety of mechanisms including (i) differentiation into other pro-tumorigenic stromal components, (ii) suppression of the immune response, (iii) promotion of angiogenesis, (iv) enhancement of an epithelial-mesenchymal transition (EMT), (v) enrichment of cancer stem-like cells (CSC), (vi) increase in tumor cell survival, and (vii) promotion of tumor metastasis. In contrast, MSCs have also been reported to have antitumorigenic functions including (i) enhancement of the immune response, (ii) inhibition of angiogenesis, (iii) regulation of cellular signaling, and (iv) induction of tumor cell apoptosis. Although literature supporting both arguments exists, most studies point to MSCs acting in a cancer supporting role within the confines of the TME. Tumor-suppressive effects are observed when MSCs are used in higher ratios to tumor cells. Additionally, MSC function appears to be tissue type dependent and may rely on cancer education to reprogram a naïve MSC with antitumor effects into a cancer-educated or cancer-associated MSC (CA-MSC) which develops pro-tumorigenic function. Further work is required to delineate the complex crosstalk between MSCs and other components of the TME to accurately assess the impact of MSCs on cancer initiation, growth, and spread.