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Short Review

Bone Regeneration Capacity through Microvesicles and Exosomes

Carla Cristina Gomes Pinheiro[1], Helena Coutinho Geiger Campos[2], Ygor Gonçalves Félix de Mattos[2] and Daniela Franco Bueno[1,2]*

[1]*Instituto de Ensino e Pesquisa Hospital Sírio-Libanês, São Paulo, São Paulo, Brazil*

[2]*Faculdade Israelita de Ciências da Saúde Albert Einstein, São Paulo, São Paulo, Brazil*

Introduction

Many orthopedic and dental complications involve the need for bone grafting procedures, such as repairing congenital defects and traumatic injuries. However, achieving complete and functional bone regeneration remains a significant challenge for orthopedic, craniofacial, and dental surgeons. Various techniques are currently used in the clinic for bone regeneration, including bone grafts, distraction osteogenesis, and guided bone regeneration [1,2].

It is known that autogenous bone grafts are considered the "gold standard" for bone regeneration. However, donor site morbidity and limited availability of bone volume restrict their practical application in clinical contexts.

Strategies for tissue engineering have been developed for the regeneration of bone defects and currently, advances in comprehending bone tissue biology and ongoing progress in tissue engineering associated with mesenchymal stem cells (MSCs), has awakened significant interest in enhancing bone tissue reconstruction [3,4]. The goal is to reduce pain and eliminate morbidities associated with surgical interventions for obtaining autologous bone, thus striving for better treatment effectiveness and a higher quality of life for the patient. Many studies are being developed using MSC [9; clinicaltrials.gov: NCT01932164].

***Corresponding author:** Daniela Franco Bueno, Instituto de Ensino e Pesquisa Hospital Sírio-Libanês, São Paulo, São Paulo, Brazil; Faculdade Israelita de Ciências da Saúde Albert Einstein, São Paulo, São Paulo, Brazil, E-mail: daniela.bueno@einstein.br

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Stem cells descending from various sources have been associated with different biomaterials (organic and inorganic) and have been used in in vitro and in vivo bone regeneration, with a varying degree of success depending on the type of stem cells used and the biomaterial's capacity to provide a compatible environment for the stem cells [5]. Among the different sources of stem cells, the ease of isolation and accessibility to obtain Dental Pulp Stem Cells (DPSCs) and Stem Cells from Human Exfoliated Deciduous Teeth (SHED) has demonstrated that these cells have advantages compared to using other sources of stem cells, because they are an abundant source of cells for regenerative medicine and involve minimal risks of complications when obtaining dental pulp [6,7].

Furthermore, it is known that dental pulp originates from the neural crest, which makes mesenchymal stem cells from this source favorable for promoting better regeneration and repair of bone tissues in the facial region, such as the jawbone and maxilla [7,8]. When the osteogenic potential of dental pulp-derived cells was compared "in vitro" to the osteogenic potential of other sources, such as the umbilical cord, dental pulp-derived MSCs demonstrate a greater potential for osteogenic differentiation and a higher expression of neural crest genes [8].

Our research group was a pioneer in conducting a cohort clinical study in which we used autologous SHED associated with a biomaterial (BIO-OSS Collagen) to promote the closure of alveolar clefts in patients with cleft lip and palate, and the treatment success was observed in this series of cases [9], as well as during the accomplishment of a multicentric clinical study conducted in specialized hospitals for the treatment of cleft lip and palate, located in different regions of Brazil. This study was conducted by our group and financed by Ministry of Health of Brazil [clinicaltrials.gov: NCT01932164].

This Research Topic aimed to broaden the knowledge on the strategies being used for bone regeneration, describing the state-of-the-art and exploring the innovative approaches in the bone restoration field. This issue currently includes six articles related to different innovative propositions associated with bone injuries.

Bone tissue is composed of bone matrix and bone cells. The bone matrix is primarily constructed from type I collagen (90%), with the remaining 10% composed of non-collagenous proteins (e.g., osteocalcin, osteonectin, bone sialoproteins, and various proteoglycans) [10,11]. Non-collagenous proteins play a role in the maturation and mineralization of the matrix and can regulate the functional activity of bone cells [10]. Although bone tissue may initially appear simple in its composition, it possesses the intrinsic ability for regeneration as part of the repair process in response to injury, as well as during skeletal development or continuous remodeling throughout adult life [11]. This process involves a complex interplay of cellular and molecular events. Therefore, intrinsic regeneration is limited and can be influenced by an individual's age and physiological conditions [12].

For an effective tissue engineering strategy for bone repair to be established, processes of osteoinduction and osteoconduction must occur at the site of the bone defect to enable its repair [12].

At the present time, the costs associated with the manufacturing of cell therapy products containing live cells for tissue regeneration, as well as the challenges in obtaining regulatory approval for these products [13], have opened up a new possibility for utilizing MSCs as "drug factories." This is because they secrete a variety of bioactive molecules and extracellular vesicles with trophic and immunomodulatory activities that contribute to the development of "cell-free" tissue engineering. This way, solely using these "medications" secreted by MSCs, either in isolation or in combination with biomaterials, will the injured tissues be regenerated [14,15].

Strategies for the Use of Extracellular Vesicles Originated From MSC in Bone Regeneration

Extracellular Vesicles (EVs) are specific cell organelles enveloped by lipids that facilitate intercellular communication by carrying proteins, nucleic acids, and certain lipids [14]. Various types of EVs have been described in the literature, including ectosomes, microvesicles, microparticles, exosomes, oncosomes, apoptotic bodies, and exomers [15]. Exosomes are a clinically relevant type of nanosized EV with diagnostic and therapeutic applications. The regulated biogenesis of exosomes and their specific cargo material targeting on recipient cells are of interest in regenerative medicine and bone tissue engineering [14,15].

The process of bone tissue regeneration/repair occurs through the sequential stages of inflammation, repair, and remodeling, involving multiple signaling pathways acting in coordination within the bone. In vivo studies analyzed the effects of transplanted MSCs in critical bone defects, a limited number of transplanted cells was observed at the defect sites, and the exact mechanism of the contribution of exogenous MSCs to the genesis of new tissue remains a topic of discussion in literature [16]. In vitro and in vivo studies suggest that transplanted MSCs may have multiple paracrine effects on endogenous cells, including immune cell modulation, angiogenic activity, recruitment of endothelial progenitor cells, stimulation of local stem cell proliferation, migration, differentiation, and anti-apoptotic effects [17-19] (Figure 1). Depending on the tissue from which MSCs were obtained, different markers can be produced, and a variety of signaling factors can be activated. All these factors and their functions must be studied to find new strategies for bone tissue regeneration [8].

Practically all types of cells secrete extracellular vesicles (EVs), which function in transferring proteins, lipids, mRNAs, miRNAs, and other non-coding RNAs, thereby modifying the activity of a neighboring or distant target cell [14]. Once EVs are released into the extracellular environment, the uptake by target cells occurs through a receptor-mediated process, internalization via endocytic uptake, or by the simple fusion of lipid bilayers between cells and vesicles [15].

In vivo studies have demonstrated that the association of EVs with biomaterials formed bone in ectopic sites [20], and in critical defects in rat calvaria, it promoted bone repair [21,22]. Preclinical studies have shown the potential use of MSC-EVs for bone tissue regeneration or treatments, where in models of osteonecrosis, there was an increase in osteocyte proliferation compared to a control group. On the other hand, in fracture models, there was an increase in callus formation and bone union, thus accelerating the formation of hypertrophic chondrocytes [23]. Table 1 represents some innovative and current studies that use tissue engineering associated with EVs for bone regeneration.

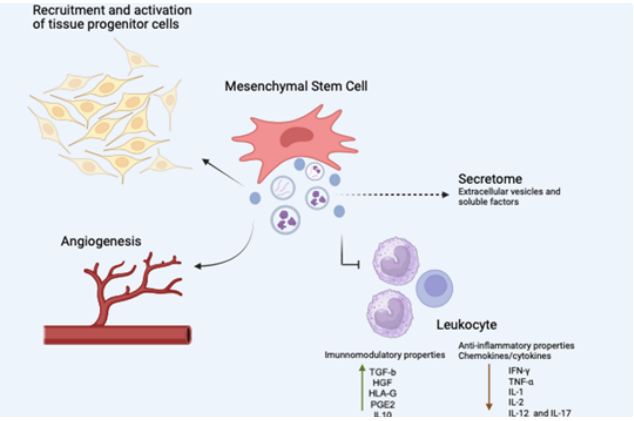

Figure 1: Mesenchymal Stem Cell and secretome that, through their extracellular vesicles, have the ability to modulate leukocytes, such as inhibition of the proliferation and activation of CD19+ B cells, CD4+ Th1 and Th17 cells, CD8+ T cells, NK cells, macrophages, monocytes and neutrophils. The secretome acts by reducing the levels of pro-inflammatory cytokines, such as IFN-γ, TNF-α, IL-1, IL-2, IL-12, and IL-17, and increasing the levels of immunoregulatory cytokines, such as TGF. -b, HGF, HLA-G, IL-10 and PGE2, which stimulates regulatory T lymphocytes. The secretome also acts in the activation and migration of progenitor cells in the tissue to be repaired and is linked to the stimulation of angiogenesis Leyendecker A, Jr. et al, 2018. Created with BioRender.com.

Author	Animal Mode	Type of Associate Scaffold	Defect	Method of Evaluation	Time of Evaluation	Outcomes
Kang Y et al. 2022	Rats	Magnesium-organic framework	Calvarial	Micro-CT, Histological and Statistical	5 to 10 Weeks	The system of prepared scaffolds generated the possibility of manipulating the slow release of Mg and GA ions , the osteogenic capacity of hBMSCs, angiogenic HUVECs and anti-inflammatory of RAW264
Chen L, et al. 2022	Rats	No Scaffold	Femoral	Micro-CT, Histological and Statistical	No specific time of evaluation	HA@SDF-1α/M2D-Exos hydrogel promotes local anti-bacterial activity, proliferation of HMSCs and HUVECs, contributing to tissue healing and repair
Su Y, et al. 2022	Rats	Synthetic polymer (Polymethylmetacrylate)	Cranial	Histological, Micro-TC, RTQ-PCR, Statistical	8 Weeks	The PPEA can release EA that induces regeneration of nerves, bones and blood vessels

Shou J et al. 2023	Mice	No Scaffold	Femoral	X-Ray, Micro-CT, Histological, Statistical	4 Weeks	3wJ-BMSCapt/M2-Exos can target BMSCs in vitro and exhibit remarked accumulation in the fracture site in vivo
Huber J, et al. 2023	Rats	No Scaffold	Femoral	DXA, BMD e RT-PCR	No specific time of evaluation	There is a lack of methods and standardization to analyze the best biomakers to detect diseases in any early stage
Pan Y et al 2023	Rats	Collagen Based Hydrogels/ Synthetic polymer	Femoral	Microscopic	No specific time of evaluation	Hydrogels Coated exomos are promising, and their role in bone tissue repair needs to be further explored

Table 1: List of Studies.

In general, the studies reported in the table have shown that, just as tissue engineering associated with cell therapy has advanced the treatment of bone defects, different tissue engineering strategies associated with EVs may be the next generation of therapy for bone tissue repair.

Challenges and Opportunities

Despite the promising use of exosomes for bone regeneration, given the potential for a "cell-free" strategy, there are still certain limitations to the transition to clinical use, particularly regarding the standardization of processes for the isolation and purification of EVs. Ultrafiltration is the most used method to isolate EVs and offers ease of sample handling, processing, and size-based selection [24]. However, large-scale production remains a challenge to overcome with current technologies.

The strategy of using EVs can provide increased patient safety by avoiding adverse reactions (lower immunogenicity) and contamination, due to their low metabolic activity, quality control processes, as well as material storage and logistics, can be simplified [25].

Final Considerations

Literature data have been demonstrating the therapeutic benefits arising from the use of exosomes in the development of bone tissue engineering. However, there is still a need for further research advancements to successfully utilize these "medications" derived from MSCs in bone tissue regeneration treatment and to effectively introduce them into the market.

In this editorial, it was possible to discover many innovative aspects, with extremely promising research fields that could change the course of the treatment of bone diseases. An important point out that innovative technologies and discoveries take time to be translated from an idea to clinical practice. Moreover, the continuing development of the mentioned studies is of key importance to create collaborative learning and reach research goals for bone treatment and, at the end, improve healthcare and patient's quality of life.

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