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Mesenchymal Stem Cells-Derived Microvesicle and the Future of Bone Grafting: A Narrative Review.

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ABSTRACT

Critically sized bone fractures cannot heal naturally without targeted intervention throughout the animal's life. Hence, advanced methods of bone reconstruction are mandatory to promote bone healing. Bone graft alternates could enhance the mechanical properties of bones and provide an endless source of bone tissue regeneration. Utilizing revascularized bone-containing free flaps is considered one of the most efficient approaches for bone reconstruction, owing to the vitality of the bone tissue involved. Nevertheless, these processes are intricate and require advanced skills, a lot of time for collection, and gradual acquisition of manual abilities over multiple years. Recently, the method involving the fusion of bone tissue engineering components and mesenchymal stem cells has shown promise, particularly in clinical settings. Mesenchymal stem cells have the capacity to produce growth factors that aid angiogenesis and recruitment of other cells that play a significant part in motivating bone tissue production and healing. This article intends to show an overview of the current state of cell therapy in engineering of animal bone tissue.

Keywords: Bone graft, Exosomes, Mesenchymal stem cell, Microvesicles.

INTRODUCTION

Bone defects are one of the main causes of disability that significantly impacts quality of life. Factors such as availability, morbidity, immunological responses, and disease transmission, pose constraints on the transplantation of living bone tissue (Burstein et al., 2000; Monaco et al., 2004). Bone tissue engineering has become a viable therapeutic approach for addressing critically sized bone defects to overcome limitations found in current clinical interventions. This approach primarily focuses on the development of devices and biomaterials that facilitate and enhance bone regeneration in a physiologically appropriate manner (Intini, 2009).

In the late 1960s, Friedenstein and his associates made the groundbreaking discovery of stem cells, which are recognized as multipotent cells, and demonstrated the preliminary illustration of

their identification. They are categorized based on their dissimilarity potential and progressive stage (Friedenstein et al., 1966; Alvarez et al., 2012; Arrigoni et al., 2013). The employment of bone marrow as the main source of stem cells remains the conventional technique, however, there has been a notable surge in the application of adipose tissue, and umbilical cord as further-sources of stem cells (de Girolamo et al., 2011; Tawfeek et al., 2023)**.**

Mesenchymal stem cells particularly of autologous source have been increasingly employed for their regenerative and therapeutic potential of diverse disorders (Fugger et al., 2020; Leng et al., 2020; Golchin, 2021; Capilla-González et al., 2022). Another crucial attributes that render them as perfect candidates for regenerative medicine include their capacity for self-renewal, extended proliferation outside the body, capability to regulate the immune response, generation of growth factors, and ability to transform into different cell lineages. (Pozzobon et al., 2014; Abbaszadeh, 2020, Margiana et al., 2022).

In the field of bone regeneration, prior studies have pointed out that these stem cells exhibit the ability to restore impaired tissue by substituting damaged cells (Matsuura et al., 2014; Huang et al., 2015). It possesses the capacity to differentiate within the respective realms of bone and cartilage into the fundamental cellular components required for regeneration such as mesenchymal stem cell -osteoblast-osteocyte and-chondroblast-chondrocyte lineages, along with endothelial cells and the monocyte-macrophage-osteoclast lineage that governs inflammation and bone resorption (Caplan, 1991; Pozzobon et al., 2014). It has been used alone or added to scaffolding material to create three-dimensional structures used to reinforce bone restoration capability (Hassibi et al., 2020; Tawfeek et al., 2023). However, the effectiveness of these approaches may be limited by regulatory considerations (Sottile et al., 2007; Turner and Knoepfler, 2016).

The advantageous impact of using mesenchymal stem cells is not only imputed to their diversity, but instead to the instigation of their defensive mechanism and inducement of natural regeneration, as well as their capacity to liberate biomolecules, such as cytokines, chemokines, and exosomes (Flower et al., 2015; Pu et al., 2020). Such active biological components facilitate the mobilization of necessary cells for the healing process. Furthermore, they impede fibrosis and cell death, improve the formation of new blood vessels, encourage cell division and of differentiation of stem cells within the tissue, and regulate the immune system, thus stimulating bone tissue renovation (Patel et al., 2008; Flower et al., 2015; Joseph Pu et al., 2020).

Although mesenchymal stem cells therapy has been supported by several studies, however, it's marked by a substantial level of hazard and delayed unfavorable outcomes. The manifestation of these consequences can be avoided by following standard manufacturing procedures after determining patient phenotype (Baranovskii et al., 2022). Over the last fifteen years, researchers have focused on utilizing extracellular vehicles (EVs) (exosomes and microvesicles) originating from various kinds of mesenchymal stem cells to surmount these restrictions (Chen et al., 2019; Takeuchi et al., 2019).

Exosomes are nanoparticles with a diameter spanning from approximately 30 to 150 nanometer and are bounded by a lipid bilayer membrane structure. They are endogenously liberated by diverse cell lines in reaction to physiological and pathological situations via cytosolic exocytosis (Abels and Breakefeld, 2016; Nooshabadi et al., 2018). They have

surfaced as a compelling contender in the field of cell-free therapy for tissue engineering. This is chiefly owed to their inherent function for transporting a wide range of active proteins, lipids, messenger RNAs, microRNAs, and other non-coding RNAs (Harding and Stahl, 1983; Pan and Johnstone, 1983; Pegtel and Gould, 2019). Moreover, they act as paracrine or endocrine mediators aiding in cell-to-cell communication. More importantly, they exhibit the same functions as their mother mesenchymal stem cells in terms of modulation of immune responses, promotion of self-repair from cells that survive injury and communication among stem cells and the injured tissue cells (Ratajczak et al., 2006; Camussi et al., 2013; Yu et al., 2014; Madrigal et al., 2014; Flower et al., 2015). Furthermore, it is more stable (can overcome the proteolytic degradation), reservable, have no risk of aneuploidy, a minor possibility of immune rejection following in vivo allogeneic administration, and consequently may provide an alternative remedy for various illnesses (Fleissner et al., 2012; Yu et al., 2014; El-Tookhy et al., 2017).

Exosomes can be harvested from various cell lines such as bone marrow, umbilical cord, adipose tissue, embryonic stem cells, or induced pluripotent stem cells. The control of the biogenesis and release of Microvesicles from the cell may be governed by various processes. Increased level of membrane blebbing development cause Microvesicles establishment (D'Souza-Schorey and Clancy, 2012). Further mechanisms have been demonstrated to influence the creation of microvesicles such as the existence of calcium in the extracellular media. Higher calcium levels can promote vesiculation from cells including erythrocytes and platelets (Crawford et al., 2010) as well as eliciting membrane phospholipid scrambling (Bucki et al., 1998). Presently, the highest ubiquitous approach to refine exosomes from conditioned media is through the use of ultracentrifugation and precipitation procedures (Elahi et al., 2020).

Recent studies have demonstrated that the effectiveness of therapies utilizing mesenchymal stem cells- derived exosomes is tantamount to that of direct stem cells therapy, while circumventing the detrimental consequences associated whole cells transplantation (Phinney and Pittenger, 2017).

In the field of regenerative medicine, various experimental models have proven the therapeutic potential of extracellular vesicles in managing tendon-bone healing (Voleti et al., 2012; Todorova et al., 2017).), osteoarthritis (Foster et al., 2016; Sabry et al., 2018), osteoporosis (Lou et al., 2019). They improve bone regeneration through angiogenesis and equilibrizing bone metabolism by assisting the variation of osteoclasts, osteoblasts, and mesenchymal stem cells (Todorova et al., 2017; Deng et al., 2019). Moreover, they are involved in the process of bone mineralization, which is fundamental for bone regeneration (Golub, 2009**)**. The angiogenic properties of exosomes have been reviewed in conjugation with distractive osteogenesis. This integrative therapy is the primary choice for managing long bone defects resulting from surgical resection or trauma, postsurgical complications and infections (Jia et al., 2019).

In conclusion, current studies have proven that mesenchymal stem cells-derived microvesicle possess a regenerative potential in the bone tissue by enhancing osteoblast differentiation and bone formation, owing to their exclusive physical and biological effects. In addition, their nano-size provides them the power to cross biological barriers.

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