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Stem Cells and Their Derivatives: Unlocking the Promising Potential of Minimally Manipulated Cells for *In Situ* Tissue Engineering

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Abstract

We've read with great interest the article by Smolinska et al. entitled "Stem Cells and Their Derivatives: An Implication for the Regeneration of Nonunion Fractures" regarding the recent scientific studies dealing with the treatment of nonunion fractures in clinical and preclinical settings using Mesenchymal Stem Cell (MSC)-based therapeutic techniques. Bone tissue regeneration is a dynamic process that involves the restoration of damaged or lost bone structure and function. Traditional approaches such as autografts and allografts, platelet rich plasma (PRP) treatment and cell therapies, have limitations, including donor site morbidity and immunologic concerns, as well as cell culture and processing requirements. In contrast, the use of minimally manipulated cells that do not require culturing has emerged as a promising alternative that offers several advantages in bone tissue regeneration.

Keywords

bone regeneration, cell culture, regenerative medicine, stem cell therapy, wound healing

Dear Editor,

We read with great interest the article entitled "Stem Cells and Their Derivatives: An Implication for the Regeneration of Nonunion Fractures" regarding the recent scientific studies dealing with the treatment of nonunion fractures in clinical and preclinical settings using MSC-based therapeutic techniques[1]. Bone tissue regeneration is a dynamic process that involves the restoration of damaged or lost bone structure and function. Traditional approaches such as autografts and allografts, platelet rich plasma (PRP) treatment and cell therapies, have limitations, including donor site morbidity and immunologic concerns, as well as cell culture and processing requirements. In contrast, the use of minimally manipulated cells that do not require culturing has emerged as a promising alternative that offers several advantages in bone tissue regeneration.

Minimally manipulated cells for bone regeneration are cell populations that are obtained and used with minimal alteration of their natural state. These cells can be derived from a variety of sources such as bone marrow, adipose tissue, and periosteum. They possess inherent regenerative capabilities and can be conveniently isolated, multiplied, and cultured in vitro. Currently, minimally manipulated cells have demonstrated substantial potential in bone tissue regeneration, particularly in cases of nonunion fractures and critical size bone defects[2].

Bone marrow–derived minimally manipulated cells exhibit superior osteogenic potential than other cell sources and possess a greater ability to differentiate into osteoblasts, leading to enhanced bone formation and regeneration[2,3]. Processing of the bone marrow primarily includes the elimination of erythrocytes and platelets with maintaining the nucleated cell-contained suspension, and may be enriched by physical methods of separation by size and mass to remove adipocytes[2,4]. The advanced techniques for isolating cells are primarily based on soft magnetic separation, which do not alter cell viability and phenotype[5].

These cells possess immunomodulatory properties that may regulate the inflammatory response at the site of injury. Minimally manipulated cells create a favorable microenvironment for bone regeneration by modulating the immune system, decreasing inflammation, and promoting the healing

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of bone tissue. The mechanisms underlying the regenerative potential of minimally manipulated cells involve paracrine signaling, cell–cell interactions, and extracellular matrix remodeling. These cells secrete various growth factors, cytokines, and chemokines that promote angiogenesis, recruit endogenous stem cells, and stimulate osteoblast differentiation and bone formation[6]. Minimally manipulated cells are primarily autologous and minimize the risk of immune rejection and disease transmission. In addition, their minimally manipulated state reduces the likelihood of genetic abnormalities or tumorigenicity, ensuring a safer therapeutic approach.

Clinical applications of minimally manipulated cells are primarily aimed to prevent graft failure or reduce the risk of implant rejection[2,7]. For the purposes of bone augmentation, these cells can be loaded into porous grafts, seeded on titanium endoprostheses, and meshed with adjuvants such as PRP[2,8]. The common result in clinical applications is that the augmentation bone area shows well-vascularized, newly formed bone-like tissue[9,10]. Currently, the widespread clinical applications of this technology appear to be limited by the poor availability of medical devices for automated cell processing with low-cost closed-loop supplies.

Despite the promising outcomes, several challenges should be overcome before minimally manipulated cells. These include optimizing cell isolation techniques, defining standardized protocols, and ensuring long-term safety and efficacy. Future research should focus on the development of advanced devices for cell isolation and delivery systems to enhance the therapeutic potential of minimally manipulated cells. The tissue engineering *in situ* promises an advanced approach for the use of minimally manipulated cells into the Operating Room[11]. Crucially, unlike the other therapeutic products containing cultured cells, application of minimally manipulated cells does not require the marketing authorization[12].

Therefore, the use of minimally manipulated cells in bone tissue regeneration represents a significant advance in regenerative medicine. Their inherent regenerative potential, immunomodulatory effects, and safety profile make them an attractive therapeutic option. Further research and clinical trials are needed to establish standardized protocols for improved bone regeneration strategies, such as protocols for cell viability assessment, cell phenotyping, cell sorting, and the secretory activity assessment. The development and standardization of these protocols is one of the key challenges in unifying the safe and effective processing and application of minimally manipulated cells.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation and analysis were performed by I.K. and D.B. The first draft of the manuscript was written by I.K., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical Approval

This article does not include any human or animal studies and ethical approval is not required.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Declaration of Conflicting Interests

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