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Editorial

Biocomplexes in bioengineering: advances in bone repair and regeneration

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Biocomplexes have emerged as one of the most representative approaches in regenerative bioengineering for bone tissue, primarily because they combine structural, biological, and functional components within a single system capable of modulating healing and stimulating new tissue formation [1]. In general terms, the concept refers to therapeutic constructs composed of cells, biomaterials, temporary scaffolds, and bioactive signals, arranged to mimic, at least in part, the microenvironment required for regeneration [1–3]. This perspective goes beyond the traditional notion of grafts or passive fillers, as it assigns an instructive role to the biomaterial, enabling it to support cell attachment, retain signaling molecules, and direct the repair process [4,5].

In regenerative medicine, this conceptual shift is particularly significant, as extensive or critical bone defects remain a major therapeutic challenge in both dentistry and reconstructive medicine [5]. Although autogenous grafts are still considered the gold standard in many cases, their use is constrained by donor site morbidity, limited tissue availability, and clinical variability [5]. Within this context, biocomplexes emerge as a rational alternative, as they aim to integrate osteoconduction, initial mechanical support, biological protection, and stability of the recipient site within a single therapeutic strategy [1,5].

The significance of these systems lies in their capacity to generate synergy among their various components. The scaffold offers a structural framework that supports cellular colonization; collagen- or fibrin-based matrices facilitate cell adhesion, retention, and the distribution of signaling molecules; and cellular or molecular elements enhance the local regenerative response through paracrine, immunomodulatory, and osteogenic mechanisms [1,5,6]. Rather than functioning as a mere combination of individual parts, these systems create a biologically active microenvironment that is

more conducive to both morphological and functional repair, particularly in defects where spontaneous regeneration is limited or unpredictable [1,7].

This concept of synergy was clearly illustrated in the proof-of-principle clinical study by Apatzidou et al., in which a biocomplex composed of autologous mesenchymal stem cells obtained from alveolar bone marrow, combined with autologous fibrin/platelet lysate and a collagen scaffold, was applied for the reconstruction of intraosseous periodontal defects [7]. The findings revealed no significant adverse events, while preserving both cell viability and the osteogenic differentiation potential of the biocomplex, along with notable clinical improvements during the follow-up period. Although overall clinical outcomes were comparable between the groups, the radiographic reduction in the Cementoenamel Junction to Bottom Defect (CEJ-BD) distance was less evident in the group treated with collagen and cell-free fibrin alone, indicating that the inclusion of cells may contribute additionally to bone regeneration [7].

Further biological analyses using the same model supported this interpretation, showing that the biocomplex-treated group exhibited a sustained reduction in TNF-α, along with increased levels of BMP-7 and OPG, and a progressive decline in the RANKL/OPG ratio over a 12-month period [8]. These results are particularly significant, as they reflect not only effective inflammatory control but also a shift in the local microenvironment toward a molecular profile more conducive to bone formation and reduced resorptive activity [8]. In this context, biocomplexes seem to function not merely as grafting materials, but rather as active modulators of the regenerative niche, creating more favorable conditions for high-quality tissue repair [7,8].

Additional clinical studies further reinforce the translational potential of this approach. Aimetti et al. described the application of a biocomplex composed of autologous dental pulp stem cells combined with a collagen sponge for the treatment of non-contained intraosseous defects, reporting reductions in probing depth, gains in clinical attachment, and radiographic defect fill after a 12-month follow-up period [2]. Similarly, earlier investigations using dental pulp–derived cells associated with collagen scaffolds demonstrated effective bone repair and adequate support for tissue regeneration, emphasizing both the accessibility of this cell source and the capacity of collagen to function as a supportive matrix for early cellular differentiation [3,4].

In the experimental setting, the findings are similarly encouraging and extend the concept of biocomplexes beyond traditional cell-based formulations. A study involving critical-size calvarial defects in rats demonstrated that the combination of synthetic tricalcium phosphate ceramic, a heterologous fibrin biopolymer, and infrared photobiomodulation enhanced bone repair and tissue formation over time [9]. Consistent with these results, both earlier and more recent studies have shown that the integration of ceramic biomaterials with fibrin, whether combined with photobiomodulation or not, can promote improved bone regeneration in critical defects, highlighting the potential of biocomplexes as a versatile regenerative platform [5,6,9].

From a morphological repair perspective, biocomplexes tend to support not only defect filling but also the preservation of local architecture and the development of a more stable organization of the newly formed tissue [7,9]. This aspect is particularly relevant in large or anatomically challenging bone defects, where clot stability, prevention of soft tissue ingrowth, and the maintenance of regenerative signals are essential for successful outcomes [2,7]. From a functional standpoint, the objective extends beyond the formation of mineralized tissue to the reestablishment of an environment capable of integrating resident cells, sustaining remodeling processes, and ensuring long-term biological functionality [7,8].

Despite the growing enthusiasm, the current body of literature still warrants careful interpretation. Many clinical studies in this area are based on case series, pilot investigations, or small sample sizes, which limits the broader applicability of the findings and complicates the demonstration of consistent statistical advantages over conventional approaches [2,7,8]. Furthermore, significant challenges remain, particularly regarding the standardization of cell sources, seeding densities, scaffold composition, surgical techniques, and evaluation criteria, all of which are essential to ensure reliable translation into clinical practice [5,7,9,10].

Nevertheless, the clinical outlook and future perspectives remain strong. The field is progressively advancing toward more standardized biocomplexes with reduced operational complexity and improved regulatory feasibility. This includes approaches based on secretomes, extracellular vesicles, cell-free therapies, bioactive matrices, and their integration with synthetic biomaterials engineered for controlled performance. In bone bioengineering, the main contribution of biocomplexes may lie precisely in demonstrating that successful regeneration does not rely on a single ideal component, but rather on the strategic integration of structure, biology, and function within constructs capable of converting a bone defect into a microenvironment supportive of true regenerative processes.

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