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Editorial

Reconstructing the Periosteal Regenerative Niche: A New Generation of Periosteal Organoids

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Received: November 04, 2026; **Published:** November 18, 2026

Abstract

The periosteum is increasingly recognized as a critical stem cell niche for skeletal regeneration. This editorial discusses and contextualizes the findings of the recent study by Qing., *et al*. which describes the development of long-term expandable periosteal organoids capable of recapitulating key features of the native regenerative microenvironment. These organoids preserve cellular heterogeneity, support hematopoietic stem cell maintenance, and retain robust bone-forming capacity following prolonged expansion. Particular emphasis is placed on the biological significance, translational potential, and current limitations of this platform, which represents an important advance toward niche-based regenerative therapies for orthopaedic tissue repair and bone regeneration.

Keywords: *Periosteal Organoids; Skeletal Regeneration; Bone Repair; Stem Cell Niche; Regenerative Orthopaedics; Hematopoietic Stem Cells; Tissue Engineering*

Abbreviations

COL1A1: Collagen Type I α 1 Chain; ECM: Extracellular Matrix; HSC: Hematopoietic Stem Cell; OCN: Osteocalcin; PDGFRα: Platelet-Derived Growth Factor Receptor Alpha; SOX9: SRY-Box Transcription Factor 9; STRO-1: Stromal Precursor Antigen-1; ZFP575: Zinc Finger Protein 575

The periosteum has emerged as one of the most important regulators of skeletal regeneration and is now recognized as a highly specialized stem cell niche rather than merely a fibrous tissue covering the cortical surface of bone. Previous experimental studies in mice have demonstrated that periosteal stem and progenitor cells play indispensable roles during fracture healing, contributing disproportionately to new bone formation compared with other skeletal progenitor populations [1,2]. Against this rapidly evolving background, the study by Jia Qing and colleagues, "Long-term expandable periosteal organoids reconstruct a functional regenerative niche that support hematopoietic stem cell maintenance and bone repair", represents a significant advance in regenerative orthopaedics because it addresses a longstanding challenge, namely the development of an expandable *in vitro* model that faithfully reproduces the biological complexity and regenerative capacity of the periosteum (Figure 1) [3].

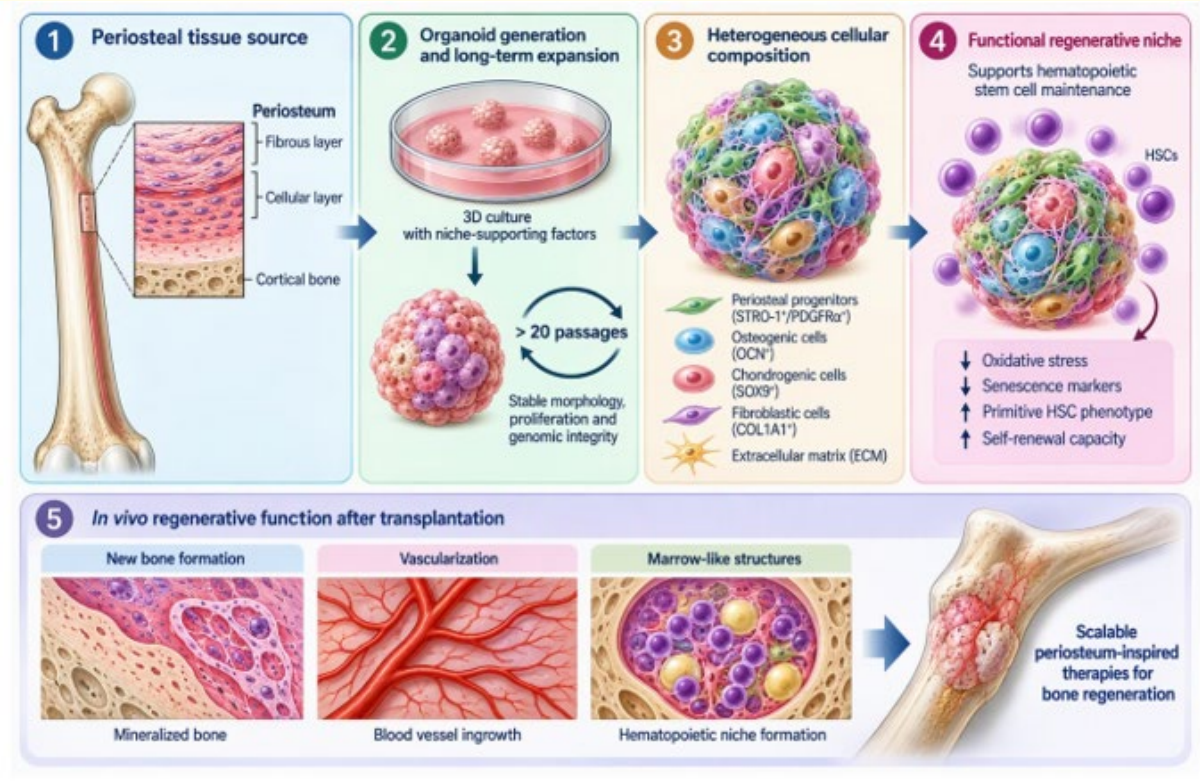


Figure 1: *Schematic overview of the generation, biological properties, and regenerative potential of periosteal organoids. (1) Native periosteal tissue is harvested from the bone surface and contains distinct fibrous and cellular layers enriched with skeletal progenitor cells. (2) Following isolation and three-dimensional culture in niche-supporting conditions, periosteal cells self-organize into long-term expandable organoids that maintain stable morphology, proliferative capacity, and genomic integrity over multiple passages. (3) The resulting organoids preserve a heterogeneous cellular composition consisting of periosteal progenitors (STRO-1+/PDGFRα+), osteogenic cells (OCN+), chondrogenic cells (SOX9+), fibroblastic stromal cells (COL1A1+), and extracellular matrix (ECM) components. (4) Functionally, periosteal organoids establish a regenerative microenvironment that supports hematopoietic stem cell (HSC) maintenance, reduces oxidative stress and cellular senescence, and promotes the preservation of primitive HSC phenotypes and self-renewal capacity. (5) Following transplantation, periosteal organoids contribute to new bone formation, vascularization, and the development of marrow-like structures, thereby recapitulating key features of the native skeletal stem cell niche. These findings highlight the translational potential of periosteum-derived organoids as scalable, periosteum-inspired therapeutic platforms for bone regeneration, skeletal tissue engineering, and niche-based regenerative medicine. Abbreviations: OCN: Osteocalcin; PDGFRα: Platelet-Derived Growth Factor Receptor α; SOX9: SRY-Box Transcription Factor 9; STRO-1: Stromal Precursor Antigen-1.*

From periosteal stem cells to functional organoids

A major strength of this work is its focus on reconstruction of the regenerative niche rather than the generation of isolated osteogenic cells. Modern regenerative medicine increasingly recognizes that successful tissue repair depends on the coordinated interaction of multiple cellular populations, extracellular matrix components, and signaling pathways. In particular, human organoid technologies have

transformed research in many biological systems because they preserve key aspects of tissue architecture and intercellular communication that are difficult to reproduce in conventional two-dimensional cultures [4]. However, skeletal organoid models (i.e. osteo-callus organoids) have lagged behind those established for intestinal, hepatic, and neural tissues. Previous attempts to generate bone or callus organoids have demonstrated encouraging regenerative properties such as the predictive design of large-scale living implants but have often been restricted by limited long-term expansion and incomplete preservation of tissue heterogeneity [5,6]. The periosteal organoid platform developed by Qing and colleagues substantially advances the field by overcoming several of these limitations [3].

One of the most impressive findings is the successful long-term propagation of periosteal organoids through more than twenty passages while maintaining stable morphology, proliferative capacity, and genomic integrity [3]. This achievement should not be underestimated. A persistent challenge in stem cell-based regenerative medicine is the progressive loss of biological potency during *ex vivo* expansion. Many progenitor cell populations undergo senescence, differentiation drift, or genetic instability with prolonged culture, thereby limiting both their scientific utility and therapeutic applicability. In contrast, the organoids described in this study retain essential characteristics of native periosteum despite extended culture periods, suggesting that the three-dimensional microenvironment preserves important regulatory mechanisms that are absent in standard monolayer systems [3].

The authors further strengthen their work through comprehensive single-cell transcriptomic analyses. In recent years, single-cell sequencing and spatial transcriptomics have revolutionized our understanding of skeletal stem cell biology, revealing an unexpectedly complex cellular landscape within bone and periosteal tissues [7,8]. The present study demonstrates that organoids maintained in long-term culture preserve multiple mesenchymal cell populations, including progenitor, osteogenic, chondrogenic, and fibroblastic subsets [3]. These populations can be represented by established lineage-associated markers such as STRO-1 and PDGFRα for periosteal progenitor cells, osteocalcin (OCN) for osteogenic cells, SOX9 for chondrogenic populations, and collagen type I α1 (COL1A1) for fibroblastic stromal cells. In particular, PDGFRα-positive periosteal progenitors have been identified as a functionally important skeletal stem cell population that contributes directly to bone formation and fracture repair [9]. Such preservation of cellular diversity is crucial because bone regeneration is not driven by a single stem cell population but rather by coordinated interactions among multiple cell types. The ability of these organoids to maintain this heterogeneity strongly supports their value as biologically relevant models of periosteal physiology.

The study also highlights current limitations of organoid technology. The authors report a gradual loss of vascular and immune cell populations during long-term culture. Although this observation does not diminish the value of the model, it underscores the continuing challenge of recreating the full complexity of native tissues *in vitro*. Immune cells, endothelial cells, and neural elements are increasingly recognized as active participants in skeletal regeneration rather than passive bystanders [3]. Future generations of periosteal organoids incorporating these additional cellular compartments may further improve physiological fidelity and translational relevance. Nevertheless, the fact that the organoids maintain robust regenerative function despite this loss suggests that essential niche characteristics reside primarily within the preserved mesenchymal populations.

Perhaps the most compelling evidence supporting the biological relevance of the model comes from transplantation experiments. Following implantation, both early- and late-passage organoids successfully generated mineralized bone, supported vascularization, and formed marrow-like structures [3]. Importantly, regenerative capacity was retained after prolonged culture, indicating that functional competence is preserved during expansion. This finding has direct translational implications because scalability remains one of the principal bottlenecks for cell-based therapies in orthopaedics. The ability to generate large numbers of functional regenerative units without significant loss of potency moves the field closer to the development of clinically feasible periosteum-inspired therapies.

Beyond bone formation: Recreating the stem cell niche

A particularly novel aspect of the study is the demonstration that periosteal organoids can support hematopoietic stem cell (HSC) maintenance. Traditionally, periosteum and bone marrow have often been studied as distinct biological compartments. More recently,

however, increasing evidence has revealed extensive interactions between skeletal stromal cells and the hematopoietic system. The bone marrow microenvironment relies on specialized stromal niches that regulate HSC quiescence, self-renewal, metabolism, and differentiation. The observation that periosteal organoids reduce oxidative stress, suppress senescence-associated markers, and maintain primitive HSC phenotypes suggests that periosteal tissues contribute more broadly to stem cell regulation than previously appreciated [3]. Importantly, the study provides a balanced assessment of this phenomenon. While organoid-supported HSCs displayed phenotypic characteristics associated with stemness, they failed to achieve robust long-term multilineage reconstitution in transplantation assays. This distinction is critical. The field of stem cell biology has repeatedly demonstrated that expression of phenotypic markers does not necessarily equate to functional stem cell activity [3]. By acknowledging this limitation, the authors provide a realistic interpretation of their findings and identify an important area for future investigation. Additional niche-derived signals, vascular interactions, or mechanical cues may be required to preserve full HSC functionality during extended culture.

Another noteworthy contribution is the identification of the zinc finger protein 575 (ZFP575) as a regulator of regenerative competence [3]. Through comparative transcriptional analyses, the authors identify genes selectively maintained within the organoid environment but lost during conventional culture. Functional experiments demonstrate that deletion of ZFP575 has relatively modest effects on organoid growth *in vitro* but markedly impairs bone formation following transplantation [3]. This is an important observation because it emphasizes that regenerative capacity cannot be inferred solely from proliferation or differentiation assays. Instead, tissue regeneration depends on specialized transcriptional programs that may only become evident during *in vivo* functional testing. The identification of ZFP575 therefore opens new avenues for investigating molecular mechanisms underlying skeletal regeneration and the maintenance of periosteal stem cell function.

Translational perspectives for orthopaedic regeneration

From a translational perspective, the defect repair experiments are among the most exciting aspects of the study. In critical-sized defect models involving long bones and the calvarium, organoid transplantation significantly enhanced bone regeneration. The observation that late-passage organoids performed comparably to early-passage organoids further emphasizes the robustness of the platform. These findings are particularly relevant because the periosteum has increasingly been recognized as a powerful therapeutic target for treating non-unions, large bone defects, and compromised fracture healing [10]. The ability to generate expandable periosteal organoids capable of promoting regeneration across multiple skeletal sites suggests broad potential applicability to orthopaedic reconstructive strategies.

Limitations of this Study

Despite these strengths, important challenges remain before clinical translation becomes feasible. The current work relies predominantly on Sprague-Dawley rat-derived periosteal cells, and it remains uncertain whether human periosteal tissues will demonstrate equivalent expansion potential and regenerative performance. Furthermore, the use of Matrigel and experimental transplantation systems may limit immediate clinical applicability. Next steps include the development of clinically compatible biomaterials, standardization of manufacturing protocols, and validation in large-animal models. In addition, challenges related to scalability, regulatory approval, reproducible manufacturing, and long-term engraftment must be addressed before therapeutic application can be considered. Mechanistically, although Jia Qing and colleagues identified ZFP575 as a key regulator of osteogenic competence within the organoid niche, the downstream molecular pathways and interactions with other regenerative signaling networks remain incompletely understood. Further studies will therefore be required to determine whether modulation of ZFP575 can enhance bone repair in clinically relevant settings. Moreover, the study primarily focused on proof-of-concept validation and biological characterization, and only limited comparisons were made with established regenerative approaches such as mesenchymal stromal cell therapies, periosteal grafts, and biomaterial-based bone tissue engineering strategies. Consequently, the relative advantages of periosteal organoids over existing therapeutic modalities remain to be fully defined. Nevertheless, the study provides compelling proof-of-principle evidence that long-term expandable periosteal organoids can preserve critical regenerative functions and may ultimately emerge as valuable therapeutic tools for orthopaedic regeneration and reconstructive medicine [3].

Concluding Remarks

In conclusion, Jia Qing and colleagues have developed an elegant and biologically sophisticated periosteal organoid platform that represents an important advance in skeletal regenerative medicine. By preserving cellular heterogeneity, supporting certain aspects of hematopoietic stem cell maintenance, identifying molecular regulators of regenerative competence, and promoting robust bone repair after prolonged expansion, the authors demonstrate the feasibility of reconstructing a functional periosteal regenerative niche *in vitro*. More broadly, this work reflects a paradigm shift within regenerative orthopaedics. Rather than engineering isolated tissues, future therapies may increasingly focus on recreating the dynamic cellular ecosystems that naturally orchestrate healing. The periosteal organoids described in this study provide a powerful experimental platform for exploring this concept and may ultimately contribute to the development of next-generation treatments for challenging orthopaedic conditions [3].

Acknowledgements

The author used OpenAI's ChatGPT-6 Sol as a writing assistance tool in the preparation of this article for English language editing and spelling corrections. The author has reviewed and edited the manuscript and takes full responsibility for the content of this manuscript. The figure in this article was conceptually designed by the author and visually developed with assistance from Microsoft 365 Copilot.

Conflict of Interest

The author serves as an Editorial Board Member of *EC Orthopaedics* but was not involved in the selection of reviewers or the editorial handling of this manuscript.

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Volume 17 Issue 9 November 2026
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