IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Role Of Stem Cells In Craniofacial Bone Regeneration: A Review

[1]DR.K. SENTHIL KUMAR, [2]DR.G.GAYATHRI SWETHA, [3]DR,K.ELAVARASU, [4]DR.C.S.C. SATISH KUMAR,

[5]DR. J. PRADEEP CHRISTOPHER

[1]PROFESSOR,[2] HOUSE SURGEON, [3]HOUSE SURGEON, [4]READER, [5]PROFESSOR AND HOD

Abstract

Craniofacial bone defects from trauma, congenital anomalies, tumors, or infections present significant reconstructive challenges due to their complex anatomy and functional-cosmetic importance. Conventional grafting techniques autografts, allografts, and xenografts are limited by donor site morbidity, immune rejection, and poor integration. Stem cell–based regenerative strategies, particularly involving mesenchymal stem cells (from bone marrow, adipose tissue, and dental sources), offer promising alternatives by enabling osteogenic differentiation, paracrine signaling, immunomodulation, and angiogenesis. Integration with biomaterials and scaffolds, including hydroxyapatite, tricalcium phosphate, natural polymers, and advanced 3D-printed or growth factor–loaded scaffolds, enhances structural support and tissue regeneration. Emerging technologies such as gene-edited stem cells, organoids, stem cell-derived exosomes, and AI-guided scaffold design enable patient-specific, biologically integrated therapies that improve functional outcomes, accelerate healing, and reduce morbidity. Stem cell–mediated craniofacial regeneration thus holds transformative potential for restoring anatomy, function, and psychosocial well-being in patients with complex craniofacial defects.

Keywords: Craniofacial regeneration, Stem cells, Bone tissue engineering, Scaffold integration, 3D bioprinting

Introduction

Craniofacial bone defects, arising from congenital anomalies, trauma, tumor resections, or infections, pose significant clinical challenges due to their impact on aesthetics, facial function, and psychosocial well-being.[1] The intricate anatomy and the dual functional cosmetic role of craniofacial structures make their reconstruction particularly demanding. Traditional grafting methods such as autografts, allografts, and xenografts have long been used to repair these defects.[2] However, each presents distinct limitations: autografts are constrained by donor site morbidity and limited availability; allografts carry risks of immune rejection and disease transmission; and xenografts often demonstrate poor integration and unpredictable resorption. Consequently, achieving complete structural and aesthetic restoration using conventional techniques remains a major obstacle in craniofacial surgery. The emergence of tissue engineering and regenerative medicine (TE/RM) has revolutionized the management of craniofacial bone loss.[3] These interdisciplinary approaches combine biomaterials, scaffolds, growth factors, and living cells to regenerate

functional tissues that closely mimic native bone. Recent advancements such as nano-engineered scaffolds, bioactive and immunomodulatory matrices, and 3D bioprinting technologies have expanded the possibilities for patient-specific and biologically compatible grafts.[4] Importantly, stem cell–based strategies have become central to this progress, offering the potential for self-renewing, osteogenic, and immunomodulatory solutions capable of overcoming the shortcomings of conventional grafts.[5] Among stem cell sources, mesenchymal stem cells particularly those derived from bone marrow, adipose tissue, and dental origins have shown remarkable potential in promoting craniofacial bone regeneration. Preclinical models have demonstrated their ability to form mineralized tissue and integrate with host bone, while early clinical studies have explored the feasibility of autologous MSC-based constructs in craniofacial defect repair. Beyond structural and functional recovery, effective craniofacial reconstruction carries profound psychosocial implications.[6] Restoring facial symmetry and integrity enhances self-image, social confidence, and emotional well-being, reducing the psychological burden associated with visible deformities. Thus, stem cell mediated regenerative therapies hold transformative potential not only in achieving biological repair but also in restoring identity and quality of life.[7] This article highlights on the Role of Stem Cells in Craniofacial Bone Regeneration.

Biology of Bone Regeneration

Bone regeneration is a complex, highly coordinated biological process that involves a series of overlapping phases inflammation, repair, and remodeling which together restore the structural and functional integrity of damaged bone. The process begins with the inflammatory phase, which is initiated immediately after injury. At this stage, a hematoma forms at the defect site, rich in signaling molecules and growth factors that recruit immune cells such as neutrophils, macrophages, and lymphocytes.[8] These cells play crucial roles in clearing necrotic debris, secreting pro-healing cytokines, and promoting angiogenesis, while also attracting progenitor cells, particularly mesenchymal stem cells (MSCs) and skeletal stem cells (SSCs), to the injury site.[9] The subsequent repair phase is characterized by the differentiation of these progenitor cells into chondrocytes and osteoblasts, facilitating new tissue formation through two distinct yet complementary ossification processes. In intramembranous ossification, occurring primarily at the periosteum, MSCs directly differentiate into osteoprogenitor cells and then osteoblasts, which secrete osteoid matrix to form woven bone without a cartilage intermediary.[10] Conversely, endochondral ossification, predominant at the endosteal or marrow regions, involves MSC differentiation into chondrocytes that produce a cartilaginous callus; this cartilage is subsequently replaced by bone as chondrocytes hypertrophy, undergo apoptosis, and are succeeded by osteoblasts that mineralize the matrix.[11] The final remodeling phase reorganizes the newly formed woven bone into mature lamellar bone, restoring mechanical strength and anatomical structure through the balanced activity of osteoblasts depositing new matrix and osteoclasts resorbing redundant bone. Central to these regenerative events are osteoprogenitor cells, derived from MSCs, which serve as the foundation for osteoblast and chondrocyte formation.[12]

Multiple signaling pathways orchestrate their differentiation, including Bone Morphogenetic Proteins (BMPs) particularly BMP-2 and BMP-9 which are potent inducers of osteogenesis and interact synergistically with Wnt/β-catenin signaling to promote osteoblast proliferation and maturation. The TGF-β (Transforming Growth Factor-β) pathway enhances the proliferation of precursor cells and potentiates BMP-mediated bone formation, while VEGF (Vascular Endothelial Growth Factor) drives angiogenesis, ensuring an adequate vascular supply essential for nutrient delivery and tissue regeneration.[13] In craniofacial bones, which primarily form through intramembranous ossification, regeneration tends to be faster and more direct, as bone develops from mesenchymal tissue without a cartilage intermediate an adaptation crucial for maintaining facial symmetry and function. However, endochondral ossification remains relevant in regions such as the cranial base, where bone replaces a cartilaginous precursor, resulting in comparatively slower regeneration.[14]

Types of Stem Cells in Craniofacial Bone Regeneration

Craniofacial bone regeneration employs a diverse array of stem cell types, each distinguished by its osteogenic potential, availability, and safety profile. Mesenchymal stem cells (MSCs) are multipotent stromal cells capable of differentiating into bone, cartilage, adipose tissue, and other lineages, and they

represent the most widely used cell type in craniofacial repair. Bone marrow-derived MSCs (BM-MSCs) are well-characterized for their robust proliferation and osteogenic capacity, making them a standard choice for bone defect reconstruction.[16] Adipose-derived MSCs (ADSCs) offer abundant, easily accessible cell sources with strong osteogenic potential, although some studies suggest slightly lower mineralization than BM-MSCs. Oral-derived MSCs, including dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), stem cells from apical papilla (SCAP), and gingiva-derived MSCs (GMSCs), exhibit high proliferation, osteogenic and neurogenic potential, and in many craniofacial-specific applications, demonstrate equal or superior performance compared to BM-MSCs and ADSCs.[17] In particular, SCAP and GMSCs have shown exceptional mineralization and colony-forming ability, making them attractive for targeted craniofacial regeneration. Induced pluripotent stem cells (iPSCs), reprogrammed from somatic cells to an embryonic-like pluripotent state, provide autologous, patient-specific solutions with the capacity to differentiate into osteoblasts via directed protocols, minimizing immunogenicity while bypassing ethical issues associated with embryonic stem cells.[18] However, iPSC therapies require careful monitoring for tumorigenicity due to genetic manipulation. Embryonic stem cells (ESCs) offer unlimited self-renewal and broad differentiation potential, including osteogenesis, yet their clinical translation is limited by ethical constraints and teratoma formation risk if cells are incompletely differentiated.[19] Additional specialized stem cells, such as periosteal cells, cranial suture stem cells (SuSCs), and neural crest-derived stem cells, provide craniofacial-specific regenerative advantages: periosteal cells contribute actively to bone repair at calvarial surfaces; SuSCs reside in suture mesenchyme with high reparative potential for cranial defects; and neural crest-derived stem cells, which can be derived from iPSCs, exhibit versatile differentiation and lineage specificity, reflecting their embryologic origin in craniofacial tissues.[20] Other sources like ADSCs and craniofacial skeletal stem cells, identified in various tissue niches, further complement the regenerative toolkit due to their self-renewal and differentiation capabilities essential for bone development and repair.[21]

Mechanisms of Stem Cell–Mediated Craniofacial Bone Regeneration

Stem cell–mediated bone regeneration in the craniofacial region relies on a complex interplay of cellular differentiation, paracrine signaling, immunomodulation, angiogenesis, and interactions with the extracellular matrix (ECM) to achieve effective repair and functional reconstruction.[22] A central mechanism involves the osteogenic differentiation of stem cells, particularly mesenchymal stem cells (MSCs), into osteoblasts and chondrocytes under the influence of local growth factors, cytokines, and key signaling pathways such as BMPs, Wnt/β-catenin, and TGF-β.[23] These differentiated cells synthesize and mineralize the bone matrix, directly contributing to tissue formation and structural restoration. Beyond direct differentiation, stem cells exert potent paracrine effects, secreting growth factors, cytokines, and chemokines including BMPs, TGF-β, PDGF, FGF, IGF, and VEGF that recruit endogenous osteoprogenitor cells, stimulate proliferation and differentiation of resident cells, and orchestrate the overall regenerative response.[24] Additionally, stem cells play immunomodulatory roles by suppressing pro-inflammatory cytokines and enhancing anti-inflammatory mediators such as IL-10 and TGF-β, thereby reducing chronic inflammation and creating a microenvironment conducive to bone healing. A critical aspect of regeneration is angiogenesis and vascular coupling, in which stem cell derived VEGF and other angiogenic factors promote endothelial cell migration, proliferation, and neovascularization, ensuring an adequate supply of oxygen, nutrients, and systemic signals necessary for sustained tissue repair.[25] Furthermore, stem cells interact closely with the extracellular matrix and biomaterial scaffolds, responding to matrix components such as collagen and glycoproteins, while scaffolds provide structural support, guide spatial organization, enhance cell adhesion and migration, and facilitate osteogenic differentiation through optimized porosity, mechanical properties, and bioactivity.[26]

Biomaterials and Scaffold Integration for Craniofacial Bone Regeneration

Effective craniofacial bone regeneration relies on the integration of biomaterials and scaffolds with stem cells and growth factors to recreate a functional bone microenvironment. Scaffold design is critical and must meet key parameters: biocompatibility to support cell adhesion, proliferation, and differentiation without provoking adverse immune responses; porosity, typically between 100–500 μm, to allow cell infiltration, nutrient diffusion, and vascularization while maintaining mechanical strength; and biodegradability, so the scaffold gradually transfers load to the regenerating tissue in synchrony with new bone formation.[27]

Common biomaterials include hydroxyapatite (HA), which mimics bone mineral and provides excellent osteoconductivity but is brittle and degrades slowly; tricalcium phosphate (TCP), which is bioresorbable and osteogenic; natural polymers like collagen, which support cell attachment and growth factor adsorption but are mechanically weak; chitosan, a biodegradable polysaccharide with antibacterial and anti-inflammatory properties; and synthetic polymers such as PLGA (poly(lactic-co-glycolic acid)), which offer tunable degradation and are often combined with ceramics to enhance strength.[28] Advanced or "smart" scaffolds further improve outcomes: growth factor–loaded scaffolds provide controlled release of osteogenic and angiogenic cues such as BMPs and VEGF; 3D-printed scaffolds allow patient-specific defect matching with precise architecture; nanostructured scaffolds mimic the extracellular matrix at the nanoscale to enhance cell attachment and differentiation; and bioactive glass supports bone bonding, stimulates osteogenic gene expression, and exhibits antibacterial properties. The success of craniofacial tissue engineering depends on the cell–scaffold–growth factor triad, where stem or progenitor cells differentiate and secrete regenerative signals, scaffolds provide structural and physical support, and growth factors orchestrate cell recruitment, proliferation, and differentiation.[29] Key signaling molecules include BMPs (especially BMP-2 and BMP-7) for osteoinduction, VEGF for angiogenesis and vascular–bone coupling, PDGF for chemotaxis and matrix remodeling, and TGF-β for regulating proliferation, differentiation, and extracellular matrix production. Scaffolds can be engineered for controlled release or gene delivery, either encapsulating growth factors or introducing DNA encoding osteogenic proteins, providing sustained local production while minimizing systemic side effects.[30]

Conclusion

Emerging technologies in craniofacial regeneration such as 3D bioprinting, gene-edited stem cells, organoids, stem cell-derived exosomes, and AI-guided scaffold design are transforming reconstructive strategies. These approaches enable personalized, biologically integrated, and functionally optimized therapies that improve anatomical fit, enhance bone regeneration, reduce donor site morbidity, and accelerate healing. Together, they represent a shift toward next-generation, patient-specific solutions that hold great promise for restoring both function and aesthetics in complex craniofacial defects.

References

1. Akintoye SO, Adisa AO, Okwuosa CU, Mupparapu M. Craniofacial disorders and dysplasias: Molecular, clinical, and management perspectives. Bone Rep. 2024 Mar 1;20:101747. doi: 10.1016/j.bonr.2024.101747. PMID: 38566929; PMCID: PMC10985038.
2. Ferraz MP. Bone Grafts in Dental Medicine: An Overview of Autografts, Allografts and Synthetic Materials. Materials (Basel). 2023 May 31;16(11):4117. doi: 10.3390/ma16114117. PMID: 37297251; PMCID: PMC10254799.
3. Zhang W, Yelick PC. Craniofacial Tissue Engineering. Cold Spring Harb Perspect Med. 2018 Jan 2;8(1):a025775. doi: 10.1101/cshperspect.a025775. PMID: 28348178; PMCID: PMC5749148.
4. Kaigler D, Pagni G, Park CH, Braun TM, Holman LA, Yi E, Tarle SA, Bartel RL, Giannobile WV. Stem cell therapy for craniofacial bone regeneration: a randomized, controlled feasibility trial. Cell Transplant. 2013;22(5):767-77. doi: 10.3727/096368912X652968. PMID: 22776413; PMCID: PMC4100608.
5. Zhao R, Yang R, Cooper PR, Khurshid Z, Shavandi A, Ratnayake J. Bone Grafts and Substitutes in Dentistry: A Review of Current Trends and Developments. Molecules. 2021 May 18;26(10):3007. doi: 10.3390/molecules26103007. PMID: 34070157; PMCID: PMC8158510.
6. Dalle Carbonare, L., Cominacini, M., Trabetti, E. *et al.* The bone microenvironment: new insights into the role of stem cells and cell communication in bone regeneration. *Stem Cell Res Ther* 16, 169 (2025). https://doi.org/10.1186/s13287-025-04288-4
7. Zizhuo Z, Hanghang L, Shibo L, En L, Xian L. Mesenchymal stem cells in craniofacial reconstruction: a comprehensive review. *Front Mol Biosci.* 2024;11:1362338. doi:10.3389/fmolb.2024.1362338
8. Khazaal H, Helman J. Narrative review: craniofacial bone regeneration—where are we now? Front Oral Maxillofac Med 2022;4:9

9. Tollemar V, Collier ZJ, Mohammed MK, Lee MJ, Ameer GA, Reid RR. Stem cells, growth factors and scaffolds in craniofacial regenerative medicine. *Genes Dis.* 2016;3(1):56-71. doi:10.1016/j.gendis.2016.01.003
10. Vignolo SM, Roth DM, Wu L, Cosgrove J, Bertassoni LE. Strategies for craniofacial tissue engineering: innovations for scalable bone regeneration. *Plast Aesthet Res*. 2025;12:20. http://dx.doi.org/10.20517/2347-9264.2025.09
11. Aghali A. Craniofacial Bone Tissue Engineering: Current Approaches and Potential Therapy. Cells. 2021 Nov 3;10(11):2993. doi: 10.3390/cells10112993. PMID: 34831216; PMCID: PMC8616509.
12. Emara A, Shah R. Recent update on craniofacial tissue engineering. *Journal of Tissue Engineering*. 2021;12. doi:10.1177/20417314211003735
13. Steppe L, Megafu M, Tschaffon-Müller MEA, Ignatius A, Haffner-Luntzer M. Fracture healing research: Recent insights. *Bone Rep.* 2023;19:101686. doi:10.1016/j.bonr.2023.101686
14. Maruyama M, Rhee C, Utsunomiya T, Zhang N, Ueno M, Yao Z, Goodman SB. Modulation of the inflammatory response and bone healing. *Front Endocrinol (Lausanne).* 2020;11:386. doi:10.3389/fendo.2020.00386.
15. Chen G, Deng C, Li YP. TGF-β and BMP signaling in osteoblast differentiation and bone formation. Int J Biol Sci. 2012;8(2):272-88. doi: 10.7150/ijbs.2929. Epub 2012 Jan 21. PMID: 22298955; PMCID: PMC3269610.
16. Zhu L, Liu Y, Wang A, Zhu Z, Li Y, Zhu C, Che Z, Liu T, Liu H and Huang L (2022) Application of BMP in Bone Tissue Engineering. Front. Bioeng. Biotechnol. 10:810880. doi: 10.3389/fbioe.2022.810880
17. Gu, C., Tang, Q., Li, L., & Chen, Y. (2024). Optimization and Implication of Adipose-Derived Stem Cells in Craniofacial Bone Regeneration and Repair. *Bioengineering*, *11*(11), 1100. https://doi.org/10.3390/bioengineering11111100
18. Zhang, G., Li, Q., Yuan, Q., & Zhang, S. (2020). Spatial Distributions, Characteristics, and Applications of Craniofacial Stem Cells. *Stem Cells International*, *2020*, 8868593. https://doi.org/10.1155/2020/8868593
19. Jiao M, Shuai T, Zhao Z, Wu Y, Yu L, Sun J, De Caro R, Macchi V, Porzionato A, Stocco E, Jin C. Categories, applications, and potential of stem cells in bone regeneration: an overview. Front Med (Lausanne). 2025 Aug 20;12:1606100. doi: 10.3389/fmed.2025.1606100. PMID: 40909447; PMCID: PMC12406871.
20. Zheng, C., Chen, J., Liu, S. *et al.* Stem cell-based bone and dental regeneration: a view of microenvironmental modulation. *Int J Oral Sci* **11**, 23 (2019). https://doi.org/10.1038/s41368-019-0060-3
21. Zheng Z, Liu H, Liu S, Luo E, Liu X. Mesenchymal stem cells in craniofacial reconstruction: a comprehensive review. Front Mol Biosci. 2024 Apr 16;11:1362338. doi: 10.3389/fmolb.2024.1362338. PMID: 38690295; PMCID: PMC11058977.
22. Gallicchio VS, Bates K. (2021) Department of Biological Sciences, College of Science, Clemson University, Clemson, South Carolina, 29636 USA. J Oral Med and Dent Res. 2(1):1-18.
23. Wan DC, Wong VW, Longaker MT. Craniofacial reconstruction with induced pluripotent stem cells. J Craniofac Surg. 2012 May;23(3):623-6. doi: 10.1097/SCS.0b013e318252f41b. PMID: 22627398; PMCID: PMC3544558.
24. Li B, Wang Y, Fan Y, Ouchi T, Zhao Z, Li L. Cranial Suture Mesenchymal Stem Cells: Insights and Advances. Biomolecules. 2021 Jul 31;11(8):1129. doi: 10.3390/biom11081129. PMID: 34439795; PMCID: PMC8392244.
25. Glaeser, J.D., Bao, X., Kaneda, G. *et al.* iPSC-neural crest derived cells embedded in 3D printable bio-ink promote cranial bone defect repair. *Sci Rep* **12**, 18701 (2022). https://doi.org/10.1038/s41598-022-22502-8
26. Murphy, M. P., Irizarry, D., Lopez, M., Moore, A. L., Ransom, R. C., Longaker, M. T., Wan, D. C., & Chan, C. (2017). The Role of Skeletal Stem Cells in the Reconstruction of Bone Defects. *Journal of Craniofacial Surgery*, *28*(5), 1136–1141. https://doi.org/10.1097/SCS.0000000000003893

27. Huang, G. T.-J., & Thesleff, I. (2013). *Stem cells in craniofacial development and regeneration*. John Wiley and Sons. https://doi.org/10.1002/9781118498026
28. Tevlin, R., Longaker, M. T., & Wan, D. C. (2020). *Skeletal Stem Cells—A Paradigm Shift in the Field of Craniofacial Bone Tissue Engineering*. *1*. https://doi.org/10.3389/FDMED.2020.596706
29. Srinivasan, A., Teo, N., Poon, K. J., Tiwari, P., Ravichandran, A., Ravichandran, A., Wen, F., Teoh, S. H., Lim, T. C., & Toh, Y.-C. (2021). Comparative Craniofacial Bone Regeneration Capacities of Mesenchymal Stem Cells Derived from Human Neural Crest Stem Cells and Bone Marrow. *ACS Biomaterials Science & Engineering*, *7*(1), 207–221. https://doi.org/10.1021/ACSBIOMATERIALS.0C00878
30. Liu, N., Lyu, X., Fan, H., Shi, J., Hu, J., & Luo, E. (2014). Animal models for craniofacial reconstruction by stem/stromal cells. *Current Stem Cell Research & Therapy*, *9*(3), 174–186. https://doi.org/10.2174/1574888X09666140213150811