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Basic Principles of Bioengineering and Regeneration

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INTRODUCTION

Although wound healing in the oral cavity occurs with minimal scarring, and oral tissue repair can take place in conditions of dental disease and infection, complex hard and soft tissue defects pose major challenges to clinicians and researchers.[1] Current methods range from simple autogenous or alloplast bone grafting to the use of growth factors with stem cells supported by biodegradable scaffolds to create elaborate 3-D constructs for tissue regeneration.[2–6] Although autogenous bone is the gold standard grafting material due to its osteogenic, osteoinductive, and osteoconductive properties, it has significant drawbacks, including a second surgical site with associated morbidity and resorption over time.[7–10] Bone graft substitutes, such as allografts, xenografts, and alloplasts, are a constant source of investigation with the goal of retaining the favorable characteristics of autogenous grafts without donor site morbidity.[11–13] Unfortunately, bone substitutes lack significant osteoinductive properties and autogenous bone grafts often create unacceptable donor site morbidity to reconstruct large or challenging craniomaxillofacial defects. Therefore, the search for methods to repair and regenerate missing or damaged craniofacial structures rather than grafting or reconstructing them is the ultimate goal of current and future research.

It is widely known that the human body has the capacity to regenerate certain tissues, such as the liver, which can regain function after significant loss.[14] Hepatocytes and liver parenchyma replicate and repopulate the missing area, restoring it to full function.[15] Unfortunately, this process of regeneration does not occur in the oral cavity or elsewhere in the body. If any oral soft or hard tissue is lost, it does not return to its original form. Instead,

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repair occurs, where damaged tissue is replaced by a fibrous network, without restoration in form or function.[16] Therefore, regeneration must take place by grafting hard and/or soft tissue. Currently, more than 1 million bone grafts are performed each year in the United States,[11] which puts a large economic burden on the health care system. Decreasing invasiveness of the procedures and eliminating the need for harvesting donor tissue, while continuing to improve outcomes are major goals for tissue engineering. As researchers become more successful with stem cell isolation and differentiation, developing improved scaffolds that are able to stimulate multiple tissue types while supporting vascularity and producing growth factors that can attain Food and Drug Administration (FDA) approval, the field of tissue engineering will continue to advance and tackle new challenges in tissue repair and regeneration.

BIOLOGICAL MECHANISMS OF WOUND REGENERATION AND REPAIR

The process of regeneration and repair begins with the formation of a wound. This leads to an inflammatory cascade that activates hemostasis. Platelets help to form an initial barrier from the outside environment and secrete growth factors from their α-granules.[17] Fibrinogen, a soluble protein, is converted into fibrin, an insoluble protein that creates a solid clot and provides a scaffold for further inflammatory cells.[18] Various cells in the environment, after being stimulated by injury, secrete chemotactic factors, such as platelet-derived growth factor (PDGF), epidermal growth factor, histamine, and von Willebrand factor.[19] The combination of these signals attracts macrophages and other leukocytes to the area, which destroy bacteria and decontaminate the area, ending the inflammatory portion of the process.[16]

The proliferation phase is marked by angiogenesis and the formation of fibrous tissue during this process; the tissue volume is re-established by fibrous repair.[20] Growth factors released from early cells in the healing wound, such as PDGF, transforming growth factor β-1 (TGF-β1), vascular endothelial growth factor (VEGF), insulin-like growth factor, basic fibroblast growth factor, and epidermal growth factor from macrophages and platelets, are responsible for beginning angiogenesis and vasculogenesis.[21,22] New blood vessels form in the granulation tissue and begin the reconstruction of the area.

After this proliferative phase, the wounded tissue undergoes remodeling and maturation. Myofibroblasts, a combination of smooth muscle cells and fibroblasts, contract to close the wound. Collagen fibers become more organized and the epithelium over the area is regenerated.[2,23] Current methods used to regenerate tissue target various portions of this pathway to achieve a desirable result, yet unfortunately the tensile strength of the healed tissue is not equal to the uninjured tissue.[24,25]

BASIC PRINCIPLES OF BONE HEALING

Missing hard tissue in the craniofacial region or oral cavity can be augmented through various procedures, each of which has benefits and pitfalls. Regardless of the material or method used, all these techniques have a few basic principles that must be followed. Many of these techniques are based on cell exclusion and cellular proliferation.[26] Cell exclusion

involves the use of a resorbable or nonresorbable membrane to limit the ingrowth of epithelial cells. Cellular proliferation is the differentiation and growth of cells in response to a certain stimulus. The success of regeneration is greatly dependent on the vascular supply available in the area. Because of this, biomaterials are frequently combined with angiogenesis stimulators.[27]

Bone augmentation is an attempt to preserve or regain bone in preparation for a prosthesis, whether an implant or denture. Various techniques are currently reported in the literature, but they all follow the same principles.[28] After extraction, it is a widely known fact that alveolar bone undergoes marked atrophy. Approximately 3.8 mm of bone is lost horizontally, whereas 1.2 mm is lost vertically.[29] To prevent this resorption, extraction socket augmentation or preservation is often performed. This procedure is generally simple and only requires particulate grafting material to serve as a scaffold to prevent soft tissue ingrowth and significantly reduces the horizontal and vertical resorption compared with tooth extraction alone.[30] Biomaterials include autografts, allografts, xenografts, and synthetic alloplasts.[31] The most commonly used materials are bovine-derived xenografts, which have proved clinically effective.[32]

Bone augmentation relies on 3 mechanisms: osteogenesis, osteoinduction, and osteoconduction. Osteogenesis involves the transplantation of osteocompetent cells to the recipient site. Only autogenous bone has osteogenic properties, especially trabecular bone with more bone marrow and increased cellularity. This is why the iliac crest is a preferred site for large craniofacial defects. Both anterior and posterior approaches provide cortical and cancellous bone and have been successful for continuity defects, alveolar clefts, and severe alveolar atrophy.[3,4,13] Osteoinduction involves chemotaxis of undifferentiated mesenchymal stem cells to the recipient site and stimulates them to become osteoblasts and form bone. Autogenous bone and specific bone morphogenic proteins (BMPs) possess osteoinductive properties. Certain demineralized allografts may have weak osteoinductive properties, but these are entirely dependent on donor variability.[33] Osteoconduction is the graft's ability to provide a scaffold, or surface, for the formation of new bone, which can be provided by most commercially available bone substitutes, including xenografts, allografts, and alloplasts. Together these mechanisms provide the formation of a stable, integrated, and vital bone structure.[2,4,34–37]

GROWTH FACTORS

The use of growth factors for tissue regeneration depends on the ability of these exogenous signals to stimulate a patient's own cells and immune system. Growth factors are secreted by multiple cell types in both temporal and spatial patterns for normal wound healing. Although wound healing is a complex process and requires multiple cells, growth factors, vascularity, and fibrin networks, clinicians and researchers are using specific growth factors to aid in bone and soft tissue repair and regeneration.[38] Because recapitulating natural wound healing is a goal of reconstructive and regenerative medicine, growth factors will definitely play a major role in current and future clinical oral and maxillofacial surgery. Although years and perhaps even decades of work have yet to be done, there has been significant progress in the field that has left commercially available recombinant growth factors and platelet

concentrates to aid in the wound-healing process. The most potent osteoinductive growth factor, BMP-2, is already FDA approved on an absorbable collagen sponge for use in spinal fusion surgery and for nonunion of tibial fractures. Since 2007, BMP-2 is also approved for maxillary sinus augmentation and localized alveolar ridge defects associated with extraction sites.[39–43] BMP-2 is chemotactic for undifferentiated mesenchymal stem cells, and up-regulates VEGF to enhance angiogenesis.[44] PDGF is the other molecule that is approved for use in dentistry, where the recombinant factor is combined with a β-tricalcium phosphate carrier for use in intrabony periodontal defects and for gingival recession.[45,46] PDGF, however, is most effective in enhancing vascularity, where it has been extremely successful in treating diabetic foot ulcers.[47,48]

Platelet concentrates, such as platelet-rich plasma and platelet-rich fibrin, are extremely popular in many surgical fields to decrease bleeding and swelling as well as aid in wound healing. Because multiple growth factors in the platelet α-granules promote vascularity, angiogenesis, enhance fibroblast proliferation, collagen synthesis, and extracellular matrix production, endothelial cell proliferation, the impetus to use platelet concentrates in bone and soft tissue grafting for enhanced tissue regeneration is well understood.[37,49,50] Few definitive studies can document significant effects on bone and soft tissue regeneration using platelet concentrates, however, thus questioning their routine use. Wound-healing adjuncts are tremendously desirable, which makes clinicians, researchers, and even patients the driving forces behind their use. The question remains if they significantly enhance wound healing and regeneration, and if they should be used in all patients as opposed to patients with compromised healing.

DISTRACTION OSTEOGENESIS

Distraction osteogenesis (DO) is a technique that creates a bone fracture and then applies a mechanical stress to stimulate bone formation.[51] In oral and maxillofacial surgery, the technique is often used to advance a retrognathic mandible or maxilla, especially in cleft palate patients or patients with significant craniofacial anomalies.[52] DO functions differently from a bone graft because it uses the principles of tension from 2 osteotomized vascular bone surfaces and the importance of neovascularization.[4,53] When the bone segments separate gradually after a latency period allows for blood clot formation, new bone forms mainly through intramembranous ossification after vessels grow on either side of the fibrous callous adjacent to osteoid tissue.[54–56] The role of the vasculature is so important that rats treated with angiogenic inhibitors had nonunion of the distracted bone segments.[57] Growth factors also play a major role in distraction; where BMP-2 and BMP-4 are expressed during the early latency stage, TGF-β is expressed until the consolidation stage, and VEGF is responsible for neovascularization.[4,58] Although DO has similar bone healing characteristics of a fracture model, DO has some complications and limitations that may prevent its widespread and routine use. Both craniofacial and alveolar distraction require patient and/or parent compliance, pose challenges controlling the vector of movement, may fail to form a uniform bone regenerate, may develop infection or inflammation from the distraction pin, and are susceptible to relapse.

SOFT TISSUE REGENERATION

Although major progress has been made in hard tissue engineering where growth factors, scaffolds, and cells are used in patients with small and large craniofacial defects, soft tissue engineering lags significantly behind.[59] Over the past decades, free gingival and connective tissue grafts have been used in clinical dentistry to treat gingival recession, increase keratinized tissue, and augment missing tissue. Soft tissue is harvested, usually from the palate, and has become highly predictable in providing patients with an esthetic solution to common mucogingival problems.[60–62] Just like for all other autogenous tissue transfers with unwanted donor site morbidity, however, a search for alternative solutions is present.

Collagen matrices are available alternatives that can be used to augment oral soft tissue deficiencies around teeth and dental implants.[63–65] These collagen matrices are treated like gingival or subepithelial connective tissue but are a nonautogenous tissue substitute. Although they have some preliminarily favorable results, the success is limited to small and simple defects. To regenerate larger and more complex volumes of soft tissue, tissue engineering principles must be followed.[59] Preliminary clinical reports as well as multiple animal studies demonstrate the development of an ex vivo–produced oral mucosal equivalent that consists of a patient's own keratinocytes cultured on a commercially available acellular freeze-dried dermis stimulated by signaling molecules in the culture media.[59,66–69] These data are particularly exciting because soft tissue defects are extremely challenging to treat, especially because they are exposed to the oral cavity with risk of contamination and infection.

STEM CELLS

Stem cell therapy has had a major impact on medicine and surgery over the past decade. In the dental field, specifically oral and maxillofacial surgery, bone marrow mesenchymal cells have been used for many years as bone marrow aspirate.[70–72] In addition, the ability to isolate and culture stem cells from dental origin, including dental pulp stem cells, stem cells from apical papilla, maxillary and mandibular bone marrow, and stem cells from exfoliated deciduous teeth that can differentiate into multiple cell types, makes the future of regenerating entire craniofacial structures seem attainable.[73–75] Stem cells are immature, undifferentiated cells that, when given the proper signals, can differentiate into any type of cell.[76] Studies in animal models already demonstrate that pulpal stem cells have the ability to regenerate alveolar bone defects.[77] Although whole-tooth regeneration is still an abstract concept, bioengineered teeth have successfully been created and implanted into pigs.[78] This new concept of stem cell differentiation and functioning regenerated tissue shows that using bioengineering to recreate missing hard and soft tissue is not far off.

SUMMARY

Bioengineering has opened the door for countless abstract ideas to rehabilitate the oral cavity and entire craniofacial structure. Clinically, there are numerous successful and predictable procedures that are used to augment and regenerate missing hard and soft tissue. Improving these current techniques, however, specifically by decreasing or omitting the need

for autogenous grafts, is the ultimate goal of clinicians and researchers. This cannot be attained unless new technologies are equivalent or superior to the gold standard of autogenous tissue. The attempt to recapitulate the complex wound-healing process of bringing the appropriate cells to the wound site that can secrete or stimulate the required growth factors with spatial and temporal precision, all on a biodegradable matrix, is an extremely challenging order. Nevertheless, the rewards of this objective cannot be overstated, and these continue to stimulate scientists all over the world to strive for success. This articles describe the past, present, and future of biomaterials and techniques in tissue regeneration and how oral and maxillofacial surgeons play a major role in helping the field progress.

References

1. Teven CM, Fisher S, Ameer GA, et al. Biomimetic approaches to complex craniofacial defects. Ann Maxillofac Surg. 2015; 5(1):4–13. [PubMed: 26389027]
2. Aghaloo, TL., Felsenfeld, AL. Principles of repair and grafting of bone and cartilage. In: Bagheri, S.Bell, R., Khan, H., editors. Current therapy in oral and maxillofacial surgery. St Louis (MO): Elsevier; 2012.
3. Costello BJ, Kumta P, Sfeir CS. Regenerative technologies for craniomaxillofacial surgery. J Oral Maxillofac Surg. 2015; 73(12 Suppl):S116–25. [PubMed: 26608139]
4. Fishero BA, Kohli N, Das A, et al. Current concepts of bone tissue engineering for craniofacial bone defect repair. Craniomaxillofac Trauma Reconstr. 2015; 8(1):23–30. [PubMed: 25709750]
5. Tevlin R, McArdle A, Atashroo D, et al. Biomaterials for craniofacial bone engineering. J Dent Res. 2014; 93(12):1187–95. [PubMed: 25139365]
6. Larsson L, Decker AM, Nibali L, et al. Regenerative medicine for periodontal and peri-implant diseases. J Dent Res. 2015; 95:255–66. [PubMed: 26608580]
7. Janicki P, Schmidmaier G. What should be the characteristics of the ideal bone graft substitute? Combining scaffolds with growth factors and/or stem cells. Injury. 2011; 42(Suppl 2):S77–81. [PubMed: 21724186]
8. Keating JF, McQueen MM. Substitutes for autologous bone graft in orthopaedic trauma. J Bone Joint Surg Br. 2001; 83(1):3–8. [PubMed: 11245534]
9. Finkemeier CG. Bone-grafting and bone-graft substitutes. J Bone Joint Surg Am. 2002; 84-A(3): 454–64. [PubMed: 11886919]
10. Chiapasco M, Zaniboni M. Failures in jaw reconstructive surgery with autogenous onlay bone grafts for pre-implant purposes: incidence, prevention and management of complications. Oral Maxillofac Surg Clin North Am. 2011; 23(1):1–15. v. [PubMed: 21167734]
11. Gruskin E, Doll BA, Futrell FW, et al. Demineralized bone matrix in bone repair: history and use. Adv Drug Deliv Rev. 2012; 64(12):1063–77. [PubMed: 22728914]
12. Acocella A, Bertolai R, Ellis E 3rd, et al. Maxillary alveolar ridge reconstruction with monocortical fresh-frozen bone blocks: a clinical, histological and histomorphometric study. J Craniomaxillofac Surg. 2012; 40(6):525–33. [PubMed: 22075326]
13. Aghaloo TL, Moy PK. Which hard tissue augmentation techniques are the most successful in furnishing bony support for implant placement? Int J Oral Maxillofac Implants. 2007; 22(Suppl): 49–70. [PubMed: 18437791]
14. Stoltz JF, de Isla N, Li YP, et al. Stem cells and regenerative medicine: myth or reality of the 21th century. Stem Cells Int. 2015; 2015:734731. [PubMed: 26300923]
15. Fausto N, Campbell JS, Riehle KJ. Liver regeneration. Hepatology. 2006; 43(2 Suppl 1):S45–53. [PubMed: 16447274]
16. Clark, R. The molecular biology of wound repair. New York: Plenum Press; 1996. Wound repair: overview and general considerations.

17. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. Physiol Rev. 2003; 83(3):835–70. [PubMed: 12843410]
18. Lord ST. Fibrinogen and fibrin: scaffold proteins in hemostasis. Curr Opin Hematol. 2007; 14(3): 236–41. [PubMed: 17414213]
19. Heldin CH, Westermark B. Mechanism of action and in vivo role of platelet-derived growth factor. Physiol Rev. 1999; 79(4):1283–316. [PubMed: 10508235]
20. Mahdavian Delavary B, van der Veer WM, van Egmond M, et al. Macrophages in skin injury and repair. Immunobiology. 2011; 216(7):753–62. [PubMed: 21281986]
21. Schliephake H. Clinical efficacy of growth factors to enhance tissue repair in oral and maxillofacial reconstruction: a systematic review. Clin Implant Dent Relat Res. 2015; 17(2):247–73. [PubMed: 23837644]
22. Harrison P, Cramer EM. Platelet alpha-granules. Blood Rev. 1993; 7(1):52–62. [PubMed: 8467233]
23. Wynn T. Common and unique mechanisms regulate fibrosis in various fibroproliferative diseases. J Clin Invest. 2007; 117(3):524–9. [PubMed: 17332879]
24. Schilling JA. Wound healing. Surg Clin North Am. 1976; 56(4):859–74. [PubMed: 959948]
25. Xue M, Jackson CJ. Extracellular matrix reorganization during wound healing and its impact on abnormal scarring. Adv Wound Care (New Rochelle). 2015; 4(3):119–36. [PubMed: 25785236]
26. Gentile P, Chiono V, Tonda-Turo C, et al. Polymeric membranes for guided bone regeneration. Biotechnol J. 2011; 6(10):1187–97. [PubMed: 21932249]
27. Oh SH, Kim TH, Chun SY, et al. Enhanced guided bone regeneration by asymmetrically porous PCL/ pluronic F127 membrane and ultrasound stimulation. J Biomater Sci Polym Ed. 2012; 23(13):1673–86. [PubMed: 21888761]
28. Guiol J, Campard G, Longis J, et al. Anterior mandibular bone augmentation techniques. Literature review Rev Stomatol Chir Maxillofac Chir Orale. 2015; 116(6):353–9. in French. [PubMed: 26586598]
29. Tan WL, Wong TL, Wong MC, et al. A systematic review of post-extractional alveolar hard and soft tissue dimensional changes in humans. Clin Oral Implants Res. 2012; 23(Suppl 5):1–21.
30. Avila-Ortiz G, Elangovan S, Kramer KW, et al. Effect of alveolar ridge preservation after tooth extraction: a systematic review and meta-analysis. J Dent Res. 2014; 93(10):950–8. [PubMed: 24966231]
31. Eppley BL, Pietrzak WS, Blanton MW. Allograft and alloplastic bone substitutes: a review of science and technology for the craniomaxillofacial surgeon. J Craniofac Surg. 2005; 16(6):981–9. [PubMed: 16327544]
32. Richardson CR, Mellonig JT, Brunsvold MA, et al. Clinical evaluation of bio-oss: a bovine-derived xenograft for the treatment of periodontal osseous defects in humans. J Clin Periodontol. 1999; 26(7):421–8. [PubMed: 10412845]
33. Boyan BD, Ranly DM, Schwartz Z. Use of growth factors to modify osteoinductivity of demineralized bone allografts: lessons for tissue engineering of bone. Dent Clin North Am. 2006; 50(2):217–28. viii. [PubMed: 16530059]
34. Siddiqui NA, Owen JM. Clinical advances in bone regeneration. Curr Stem Cell Res Ther. 2013; 8(3):192–200. [PubMed: 23317467]
35. Roberts TT, Rosenbaum AJ. Bone grafts, bone substitutes and orthobiologics: the bridge between basic science and clinical advancements in fracture healing. Organogenesis. 2012; 8(4):114–24. [PubMed: 23247591]
36. Einhorn TA. The cell and molecular biology of fracture healing. Clin Orthop Relat Res. 1998; 355(Suppl):S7–21.
37. Ulma, R., Aghaloo, TL., Freymiller, E. Wound healing. In: Fonseca, R.HDBPowers, M., et al., editors. Oral and maxillofacial trauma. St. Louis (MO): Elsevier; 2013. p. 9
38. Aghaloo, TL., Pi-Anfruns, J., Simel, O., et al. Growth factors in implant dentistry. In: Moy, P.Beumer, J., Shah, K., editors. Fundamentals of implant dentistry. Chicago: Quintessence; 2016.

39. Boyne PJ, Lilly LC, Marx RE, et al. De novo bone induction by recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillary sinus floor augmentation. J Oral Maxillofac Surg. 2005; 63(12):1693–707. [PubMed: 16297689]
40. Triplett RG, Nevins M, Marx RE, et al. Pivotal, randomized, parallel evaluation of recombinant human bone morphogenetic protein-2/absorbable collagen sponge and autogenous bone graft for maxillary sinus floor augmentation. J Oral Maxillofac Surg. 2009; 67(9):1947–60. [PubMed: 19686934]
41. Fiorellini JP, Howell TH, Cochran D, et al. Randomized study evaluating recombinant human bone morphogenetic protein-2 for extraction socket augmentation. J Periodontol. 2005; 76(4):605–13. [PubMed: 15857102]
42. Wozney JM. Overview of bone morphogenetic proteins. Spine (Phila Pa 1976). 2002; 27(16 Suppl 1):S2–8. [PubMed: 12205411]
43. Yamaguchi A, Komori T, Suda T. Regulation of osteoblast differentiation mediated by bone morphogenetic proteins, hedgehogs, and Cbfa1. Endocr Rev. 2000; 21(4):393–411. [PubMed: 10950158]
44. Spagnoli DB, Marx RE. Dental implants and the use of rhBMP-2. Oral Maxillofac Surg Clin North Am. 2011; 23(2):347–61. vii. [PubMed: 21492806]
45. Nevins M, Giannobile WV, McGuire MK, et al. Platelet-derived growth factor stimulates bone fill and rate of attachment level gain: results of a large multicenter randomized controlled trial. J Periodontol. 2005; 76(12):2205–15. [PubMed: 16332231]
46. Howell TH, Fiorellini JP, Paquette DW, et al. A phase I/II clinical trial to evaluate a combination of recombinant human platelet-derived growth factor-BB and recombinant human insulin-like growth factor-I in patients with periodontal disease. J Periodontol. 1997; 68(12):1186–93. [PubMed: 9444594]
47. Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. Plast Reconstr Surg. 2006; 117(7 Suppl):143S–9S. discussion: 150S–1S. [PubMed: 16799381]
48. Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. Diabetes Care. 1998; 21(5):822–7. [PubMed: 9589248]
49. Barrientos S, Stojadinovic O, Golinko MS, et al. Growth factors and cytokines in wound healing. Wound Repair Regen. 2008; 16(5):585–601. [PubMed: 19128254]
50. Marx, RE. Platelet-rich plasma: a source of multiple autologous growth factors for bone grafts. In: Lynch, SE.Genco, RJ., Marx, RE., editors. Tissue Engineering: applications in maxillofacial surgery and periodontics. Chicago: Quintessence; 1999. p. 71
51. Dhaliwal K, Kunchur R, Farhadieh R. Review of the cellular and biological principles of distraction osteogenesis: an in vivo bioreactor tissue engineering model. J Plast Reconstr Aesthet Surg. 2016; 69:e19–26. [PubMed: 26725979]
52. Chin M. The role of distraction osteogenesis in oral and maxillofacial surgery. J Oral Maxillofac Surg. 1998; 56(6):805–6.
53. Ai-Aql ZS, Alagl AS, Graves DT, et al. Molecular mechanisms controlling bone formation during fracture healing and distraction osteogenesis. J Dent Res. 2008; 87(2):107–18. [PubMed: 18218835]
54. Aronson J, Good B, Stewart C, et al. Preliminary studies of mineralization during distraction osteogenesis. Clin Orthop Relat Res. 1990; (250):43–9.
55. Delloye C, Delefortrie G, Coutelier L, et al. Bone regenerate formation in cortical bone during distraction lengthening. An experimental study. Clin Orthop Relat Res. 1990; (250):34–42. [PubMed: 2293942]
56. Percival CJ, Richtsmeier JT. Angiogenesis and intra-membranous osteogenesis. Dev Dyn. 2013; 242(8):909–22. [PubMed: 23737393]
57. Fang TD, Salim A, Xia W, et al. Angiogenesis is required for successful bone induction during distraction osteogenesis. J Bone Miner Res. 2005; 20(7):1114–24. [PubMed: 15940364]

58. Choi IH, Chung CY, Cho TJ, et al. Angiogenesis and mineralization during distraction osteogenesis. J Korean Med Sci. 2002; 17(4):435–47. [PubMed: 12172035]
59. Kim RY, Fasi AC, Feinberg SE. Soft tissue engineering in craniomaxillofacial surgery. Ann Maxillofac Surg. 2014; 4(1):4–8. [PubMed: 24987591]
60. Shah R, Thomas R, Mehta DS. Recent modifications of free gingival graft: a case series. Contemp Clin Dent. 2015; 6(3):425–7. [PubMed: 26321849]
61. Bassetti RG, Stähli A, Bassetti MA, et al. Soft tissue augmentation procedures at second-stage surgery: a systematic review. Clin Oral Investig. 2016; 20:1369–87.
62. Thoma DS, Buranawat B, Hämmerle CH, et al. Efficacy of soft tissue augmentation around dental implants and in partially edentulous areas: a systematic review. J Clin Periodontol. 2014; 41(Suppl 15):S77–91. [PubMed: 24641003]
63. Thoma DS, Zeltner M, Hilbe M, et al. Randomized controlled clinical study evaluating effectiveness and safety of a volume-stable collagen matrix compared to autogenous connective tissue grafts for soft tissue augmentation at implant sites. J Clin Periodontol. 2016; 43:874–85. [PubMed: 27310522]
64. McGuire MK, Scheyer ET. Long-term results comparing xenogeneic collagen matrix and autogenous connective tissue grafts with coronally advanced flaps for treatment of dehiscence-type recession defects. J Periodontol. 2016; 87(3):221–7. [PubMed: 26469812]
65. McGuire MK, Scheyer ET. Randomized, controlled clinical trial to evaluate a xenogeneic collagen matrix as an alternative to free gingival grafting for oral soft tissue augmentation. J Periodontol. 2014; 85(10):1333–41. [PubMed: 24597764]
66. Izumi K, Song J, Feinberg SE. Development of a tissue-engineered human oral mucosa: from the bench to the bed side. Cells Tissues Organs. 2004; 176(1–3):134–52. [PubMed: 14745242]
67. Izumi K, Feinberg SE. Skin and oral mucosal substitutes. Oral Maxillofac Surg Clin North Am. 2002; 14(1):61–71. [PubMed: 18088611]
68. Peramo A, Marcelo CL, Feinberg SE. Tissue engineering of lips and mucocutaneous junctions: in vitro development of tissue engineered constructs of oral mucosa and skin for lip reconstruction. Tissue Eng Part C Methods. 2012; 18(4):273–82. [PubMed: 22067042]
69. Izumi K, Terashi H, Marcelo CL, et al. Development and characterization of a tissue-engineered human oral mucosa equivalent produced in a serum-free culture system. J Dent Res. 2000; 79(3): 798–805. [PubMed: 10765951]
70. Marx RE, Harrell DB. Translational research: The CD34+ cell is crucial for large-volume bone regeneration from the milieu of bone marrow progenitor cells in craniomandibular reconstruction. Int J Oral Maxillofac Implants. 2014; 29(2):e201–9. [PubMed: 24683583]
71. Soltan M, Smiler DG, Gailani F. A new “platinum” standard for bone grafting: autogenous stem cells. Implant Dent. 2005; 14(4):322–5. [PubMed: 16361880]
72. Smiler DG, Soltan M, Soltan C, et al. Growth factors and gene expression of stem cells: bone marrow compared with peripheral blood. Implant Dent. 2010; 19(3):229–40. [PubMed: 20523179]
73. Zhao H, Chai Y. Stem cells in teeth and craniofacial bones. J Dent Res. 2015; 94(11):1495–501. [PubMed: 26350960]
74. Sakai VT, Zhang Z, Dong Z, et al. SHED differentiate into functional odontoblasts and endothelium. J Dent Res. 2010; 89(8):791–6. [PubMed: 20395410]
75. Akintoye SO, Lam T, Shi S, et al. Skeletal site-specific characterization of orofacial and iliac crest human bone marrow stromal cells in same individuals. Bone. 2006; 38(6):758–68. [PubMed: 16403496]
76. Girlovanu M, Susman S, Soritau O, et al. Stem cells -biological update and cell therapy progress. Clujul Med. 2015; 88(3):265–71. [PubMed: 26609255]
77. Huojia M, Wu Z, Zhang X, et al. Effect of Dental Pulp Stem Cells (DPSCs) in repairing rabbit alveolar bone defect. Clin Lab. 2015; 61(11):1703–8. [PubMed: 26731996]
78. Yang KC, Kitamura Y, Wu CC, et al. Tooth germ-like construct transplantation for whole-tooth regeneration: an in vivo study in the miniature pig. Artif Organs. 2016; 40:E39–50. [PubMed: 26582651]

KEY POINTS

- Research into fabricating allografts may potentially reduce the need for autografts, thus reducing donor site morbidity.
- Different systems of delivery of stem cells have been explored with varying results.
- The use of growth factors along with stem cells and scaffolding systems has been shown to aid in grafting procedures.