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BONE GRAFTING STIMULATES PRECURSOR CELLS TO DIFFERENTIATE AND PROMOTE REGENERATION

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ABSTRACT

Transplant rejection occurs when the host's immune system attacks the transplanted organ. However, the transplanted organ can also reject the recipient host. In this case, the reaction is called "graft versus host" (GVH). There are three types of transplant rejection: acute, hyperacute, and chronic. In chronic rejection, activation of the immune system leads to fibrosis of the blood vessels of the transplanted organ and loss of the organ. Bone marrow transplantation is a very useful and life-saving procedure, but it requires careful planning and ongoing monitoring to manage the risks. To reduce the risk of rejection, the donor must have human leukocyte antigen (HLA) that matches with the recipient, and the recipient must be treated with immunosuppressants. Bone graft materials attract and stimulate precursor cells from surrounding tissues and the bloodstream. These materials act as a physical scaffold to participate in the growth and formation of new bone by providing a surface for attachment and causing osteoblasts to proliferate, which is an important process in implantology and periodontal therapies. Osteoblasts play a crucial role in bone grafting and regeneration, and successful implant osseointegration is highly dependent on osteoblasts depositing new bone matrix around the implant surface. The wnt/β-catenin pathway promotes biological effects on osteoblasts and enhances bone formation and regeneration. Bone morphogenetic proteins (BMPs) 2 and 7 are strong inducers of osteoblast differentiation from mesenchymal stem cells and runt-related transcription factor 2 (RUNX2) is a good regulator of osteoblast differentiation. In periodontitis, an altered level of cytokines occurs, leading to inflammatory phenomena involving osteoblasts. Here, we discuss bone grafting in dentistry and the problems related to rejection, periodontal tissue regeneration, and the role of osteoblasts.

KEYWORDS: *Bone graft, transplant, rejection, bone marrow, immunity, dentistry*

INTRODUCTION

Transplant rejection occurs when a transplant recipient's immune system attacks the new organ, recognizing it as foreign (1). The mechanism of attack is similar to that which occurs when a microorganism enters the human body. Rejection is classified as acute, hyperacute, or chronic. Acute rejection occurs in a short time (minutes) and is due to an immune reaction that occurs between lymphocytes and the foreign antigen shown by the transplanted organ (2).

The transplanted organ can also be responsible for rejection, when it carries out a reaction towards the recipient (host), which is called graft versus host (GVH). In this case, the donor cells fail to engraft properly in the recipient's body. Rejection is more common in allogeneic transplants because of different immune compatibility. Hyperacute rejection usually occurs five to ten days after surgery and, if not treated with immunosuppressants, the transplanted organ is rejected

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(3). Chronic rejection can occur long after the transplant and presents persistent activation of the immune system, fibrosis of the blood vessels of the transplanted organ, and loss of the organ (4). The use of immunosuppressants can not only prolong the rejection process but can also lead to the success of the transplant (5).

Transplantation can be performed not only with organs, but also with bone marrow stem cells. This is a complex medical procedure used to treat a variety of diseases, including leukemia and lymphoma, aplastic anemia, and some genetic or immune system diseases (6). These therapeutic treatments are crucial, but they often have complications, including rejection of the bone marrow (7). Bone marrow transplantation is a life-saving procedure for many conditions, but it requires careful planning and ongoing monitoring to manage risks. Causes of rejection include a human leukocyte antigen (HLA) mismatch between donor and recipient, which increases the risk of rejection (8). Pre-existing antibodies in the recipient or insufficient immunosuppression can also lead to rejection.

DISCUSSION

In dentistry, bone graft materials recruit precursor cells from surrounding tissues and the bloodstream (9). The graft material acts as a physical scaffold and participates in the growth and formation of new bone by providing a surface for osteoblasts to attach and proliferate. The precursor cells of the bone-forming osteoblasts are stimulated by certain graft materials and growth factors, causing osteogenesis (10). "Fresh" viable osteoblasts, which are present in autografts, contribute directly to the formation of new bone.

To make a satisfactory graft occur, an appropriate choice of graft is needed. There are various types of grafts such as autograft directly from the patient, or allograft from the donor (11). In the first case, the cells are alive and natural growth factors are activated, which offers excellent results. In the second case, treatments are used to maintain osteoconductive and, in some cases, osteoinductive properties. There is also a third type of graft, the xenograft, with osteoconductive material from other species. In this case, there is a high probability of rejection (12).

Synthetic grafts such as bioceramics are widely used today and are combined with active biological material to obtain a good osteoinductive effect (13). To obtain a satisfactory result, it is necessary to use biological growth factors. Transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF) are crucial for the differentiation and formation of new vessels (angiogenesis) (14). In addition, the use of some cytokines that regulate signaling are important for the activity of precursor cells and osteoblasts.

Osteoblasts

In dentistry, bone regeneration is governed by osteoblasts, which are important in implantology and periodontal therapies (15). Osteoblasts are precursor cells in bone formation and their activity is essential for maintaining healthy bone structure and function (16). In dentistry, osteoblasts play a fundamental role in bone grafting and regeneration, which are methods for implant placement and reconstructive surgery (17). The success of implant osseointegration depends greatly on osteoblasts that deposit new bone matrix around the implant surface (18).

In periodontal disease, there is a loss of bone regeneration that requires the activation and proliferation of osteoblasts. Osteoblasts are also important in orthodontics where tooth movement involves a balance between bone resorption by osteoclasts and bone formation managed by osteoblasts (19). Osteoblast differentiation and activity is due to the wnt/β-catenin pathway that promotes biological effects on osteoblasts, such as increased bone formation and regeneration (20).

Bone Morphogenetic Protein (BMP) 2 and 7 are strong inducers of osteoblast differentiation from mesenchymal stem cells (21). BMP2 is a protein present in the human body that promotes the growth of new bone. BMP-2 has been studied for several years for its ability to repair bone, almost completely eliminating the need for bone grafts from other parts of the body. This protein has been approved by the FDA and is used in bone grafting. BMP-7 is a member of the TGF-β family, which is widely expressed during fetal life. It plays an important role in stimulating bone synthesis and can be used for therapeutic purposes (22). Its active ingredient is called heptotermin alpha, a copy of BMP-7, and has the ability to induce bone production in recent fractures (23).

A good regulator of osteoblast differentiation is runt-related transcription factor 2 (RUNX2) (24). It is important for mesenchymal stem cells in the differentiation of osteoblasts. Osteoblasts secrete type I collagen, which forms the organic framework of bone (25). Osteocalcin and alkaline phosphatase are proteins involved in matrix maturation and mineralization (26). Additionally, in orthodontics, osteoblasts respond to mechanical insults via integrin-mediated pathways, promoting bone remodeling (27). Chronic inflammatory phenomena often occur in periodontitis and can compromise the function of osteoblasts by altering the levels of TNF, IL-1β and IL-6 cytokines and by acting on the interaction between osteoblasts and the implant (28,29). Other cytokines such as VEGF and TGF-β play a role in angiogenesis and bone formation at implant sites (30).

CONCLUSIONS

Bone grafting is characterized by its ability to increase both bone volume and bone density. In addition, it improves the stability of dental implants and the regeneration of periodontal tissues. These reactions are due to the body's natural ability to regenerate bone through the stimulation and differentiation of precursor cells. Today, bone grafting is a valuable and indispensable tool in dentistry.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Buser D, Urban I, Monje A, Kunrath MF, Dahlin C. Guided bone regeneration in implant dentistry: Basic principle, progress over 35 years, and recent research activities. *Periodontology 2000*. 2023;93(1):9-25. doi:https://doi.org/10.1111/prd.12539
2. Klos D, Orság J, Loveček M, et al. Emergency surgical treatment of complicated acute pancreatitis after kidney transplantation with acute rejection: Case report and literature review. *Annals of Medicine & Surgery*. 2016;8:14-17. doi:https://doi.org/10.1016/j.amsu.2016.04.022
3. Lu T, Yang B, Wang R, Qin C. Xenotransplantation: Current Status in Preclinical Research. *Frontiers in Immunology*. 2020;10. doi:https://doi.org/10.3389/fimmu.2019.03060
4. Kitamura K, Buchholz BM, Abu-Elmagd K, Kalff JC, Schäfer N, von Websky MW. Chronic rejection after intestinal transplantation: A systematic review of experimental models. *Transplantation Reviews*. 2019;33(3):173-181. doi:https://doi.org/10.1016/j.trre.2019.04.001
5. Clavien PA, Muller X, de Oliveira ML, Dutkowski P, Sanchez-Fueyo A. Can immunosuppression be stopped after liver transplantation? *The Lancet Gastroenterology & Hepatology*. 2017;2(7):531-537. doi:https://doi.org/10.1016/s2468-1253(16)30208-4
6. Muzio LL, Stefano Tetè, Mastrangelo F, et al. A novel mutation of gene CBFA1/RUNX2 in cleidocranial dysplasia. *PubMed*. 2007;37(2):115-120.
7. Simkin PA. Marrow fat may distribute the energy of impact loading throughout subchondral bone. *Rheumatology*. 2017;57(3):414-418. doi:https://doi.org/10.1093/rheumatology/kex274
8. Patterson J, Prentice H, Brenner MK, et al. Graft rejection following HLA matched T-lymphocyte depleted bone marrow transplantation. *British Journal of Haematology*. 2008;63(2):221-230. doi:https://doi.org/10.1111/j.1365-2141.1986.tb05544.x
9. Ho-Shui-Ling A, Bolander J, Rustom LE, Johnson AW, Luyten FP, Picart C. Bone regeneration strategies: Engineered scaffolds, bioactive molecules and stem cells current stage and future perspectives. *Biomaterials*. 2018;180:143-162. doi:https://doi.org/10.1016/j.biomaterials.2018.07.017
10. Hosseini FS, Nair LS, C.T. Laurencin. Inductive Materials for Regenerative Engineering. *Journal of Dental Research*. 2021;100(10):1011-1019. doi:https://doi.org/10.1177/00220345211010436
11. Fillingham Y, Jacobs J. Bone grafts and their substitutes. *The Bone & Joint Journal*. 2016;98-B(1_Supple_A):6-9. doi:https://doi.org/10.1302/0301-620x.98b.36350
12. Khan SN, Cammisa FP, Sandhu HS, Diwan AD, Girardi FP, Lane JM. The Biology of Bone Grafting. *Journal of the American Academy of Orthopaedic Surgeons*. 2005;13(1):77-86. doi:https://doi.org/10.5435/00124635-200501000-00010
13. Kankilic B, Köse S, Korkusuz P, Timuçin M, Korkusuz F. Mesenchymal Stem Cells and Nano-Bioceramics for Bone Regeneration. *Current Stem Cell Research & Therapy*. 2016;11(6):487-493. doi:https://doi.org/10.2174/1574888x10666150202150518
14. Shi Y, Yu P, Zeng D, et al. Suppression of vascular endothelial growth factor abrogates the immunosuppressive capability of murine gastric cancer cells and elicits antitumor immunity. *The FEBS Journal*. 2014;281(17):3882-3893. doi:https://doi.org/10.1111/febs.12923
15. Tetè S, Mastrangelo F, Traini T, et al. A Macro- and Nanostructure Evaluation of a Novel Dental Implant. *Implant Dentistry*. 2008;17(3):309-320. doi:https://doi.org/10.1097/id.0b013e318182d494

16. Mizoguchi T, Ono N. The diverse origin of bone-forming osteoblasts. *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research*. 2021;36(8):1432-1447. doi:https://doi.org/10.1002/jbmr.4410
17. Mastrangelo F, Gastaldi G, Vinci R, et al. Immediate Postextractive Implants With and Without Bone Graft. *Implant Dentistry*. 2018;27(6):638-645. doi:https://doi.org/10.1097/id.0000000000000816
18. Vandamme K, Naert I, Jozef Vander Sloten, Puers R, Duyck J. Effect of Implant Surface Roughness and Loading on Peri-Implant Bone Formation. *Journal of Periodontology*. 2008;79(1):150-157. doi:https://doi.org/10.1902/jop.2008.060413
19. Li Y, Zhan Q, Bao M, Yi J, Li Y. Biomechanical and biological responses of periodontium in orthodontic tooth movement: up-date in a new decade. *International Journal of Oral Science*. 2021;13(1). doi:https://doi.org/10.1038/s41368-021-00125-5
20. Shen G, Ren H, Shang Q, et al. Foxf1 knockdown promotes BMSC osteogenesis in part by activating the Wnt/β-catenin signalling pathway and prevents ovariectomy-induced bone loss. *EBioMedicine*. 2020;52:102626-102626. doi:https://doi.org/10.1016/j.ebiom.2020.102626
21. Sánchez-Duffhues G, Hiepen C, Knaus P, ten Dijke P. Bone morphogenetic protein signaling in bone homeostasis. *Bone*. 2015;80:43-59. doi:https://doi.org/10.1016/j.bone.2015.05.025
22. Cho K, Kim NH, Seo SH, et al. A micellized bone morphogenetic protein-7 prodrug ameliorates liver fibrosis by suppressing transforming growth factor-β signaling. *PubMed*. 2022;12(2):763-778.
23. Patel AD. Bone morphogenetic proteins in orthopaedic trauma: recent clinical findings with human bone morphogenetic protein-2 (rhBMP-2). *Current Medical Research and Opinion*. 2006;22(sup1):S1-S5. doi:https://doi.org/10.1185/030079906x80567
24. Ren C, Xu Y, Liu H, et al. Effects of runt-related transcription factor 2 (*RUNX2*) on the autophagy of rapamycin-treated osteoblasts. *Bioengineered*. 2022;13(3):5262-5276. doi:https://doi.org/10.1080/21655979.2022.2037881
25. Lu Y, Kamel-El Sayed SA, Wang K, et al. Live Imaging of Type I Collagen Assembly Dynamics in Osteoblasts Stably Expressing GFP and mCherry-Tagged Collagen Constructs. *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research*. 2018;33(6):1166-1182. doi:https://doi.org/10.1002/jbmr.3409
26. Diemar SS, Møllehave LT, Quardon N, et al. Effects of age and sex on osteocalcin and bone-specific alkaline phosphatase—reference intervals and confounders for two bone formation markers. *Archives of Osteoporosis*. 2020;15(1). doi:https://doi.org/10.1007/s11657-020-00715-6
27. Li J, Zhao Z, Wang J, Chen G, Yang J, Luo S. The role of extracellular matrix, integrins, and cytoskeleton in mechanotransduction of centrifugal loading. *Molecular and Cellular Biochemistry*. 2007;309(1-2):41-48. doi:https://doi.org/10.1007/s11010-007-9641-0
28. Sammartino G, Marenzi G, Tammaro L, et al. Anti-inflammatory drug incorporation into polymeric nano-hybrids for local controlled release. *PubMed*. 2006;18(3 Suppl):55-62.
29. David JP, Schett G. TNF and Bone. *Current Directions in Autoimmunity*. 2010;11:135-144. doi:https://doi.org/10.1159/000289202
30. Kostiv RE, N. Yu. Matveeva, Kalinichenko SG. Localization of VEGF, TGF-β1, BMP-2, and Apoptosis Factors in Hypertrophic Nonunion of Human Tubular Bones. *Bulletin of Experimental Biology and Medicine*. 2022;173(1):160-168. doi:https://doi.org/10.1007/s10517-022-05513-3