2-26-2018

The Distinctive Jaw and Alveolar Bone Regeneration

Sunday O. Akintoye
University of Pennsylvania

Recommended Citation

Akintoye, S. O. (2018). The Distinctive Jaw and Alveolar Bone Regeneration. *Oral Diseases, 24* (1-2), http://dx.doi.org/10.1111/odi.12761

The Distinctive Jaw and Alveolar Bone Regeneration

Abstract

The skeletal system is structurally and functionally unique. It can be referred to as connective tissue that lost its ability to resist mineralization as mineralization in any other connective tissues is heterotopic. In addition to providing support for muscular attachments, the skeletal system protects nerves and harbors the hematopoietic and mesenchymal stem cells within the bone marrow compartment. However, there are distinct phenotypic and functional differences between the orofacial skeleton compared to axial and appendicular skeleton. How different is the jaw bone from other non-craniofacial bones? Interestingly, developmental, biological, and clinical outcomes point to distinctive features that make the jaw bone unique.

Keywords

orofacial, mesenchymal stem cells, graft, regeneration

Disciplines

Dentistry

Received: 9 August 2017 | Accepted: 14 August 2017

DOI: 10.1111/odi.12761

PROF SCULLY MEMORIAL ISSUE

WILEY ORAL DISEASES

The distinctive jaw and alveolar bone regeneration

SO Akintoye

Department of Oral Medicine, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA, USA

Correspondence
Sunday O. Akintoye, Department of Oral Medicine, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA, USA.
Email: akintoye@upenn.edu

The skeletal system is structurally and functionally unique. It can be referred to as connective tissue that lost its ability to resist mineralization as mineralization in any other connective tissues is heterotopic. In addition to providing support for muscular attachments, the skeletal system protects nerves and harbors the hematopoietic and mesenchymal stem cells within the bone marrow compartment. However, there are distinct phenotypic and functional differences between the orofacial skeleton compared to axial and appendicular skeleton. How different is the jaw bone from other non-craniofacial bones? Interestingly, developmental, biological, and clinical outcomes point to distinctive features that make the jaw bone unique.

KEYWORDS
orofacial, mesenchymal stem cells, graft, regeneration

1 | JAW BONES ARE DEVELOPMENTALLY SITE-SPECIFIC

Molecular mechanisms that regulate craniofacial bone development are different and unique from those of axial and appendicular bones (Helms & Schneider, 2003; Ramaesh & Bard, 2003). The maxilla and mandible develop embryologically from neural crest cells of the neuroectoderm, while the axial and appendicular bones develop from the mesodermal germ layer. (Chai & Maxson, 2006; Cordero et al., 2011). While the axial and appendicular bones undergo endochondral ossification, the orofacial bones have dual intramembranous and endochondral ossification patterns and the mandible forms from the template of the Meckel's cartilage. (Helms & Schneider, 2003; Ramaesh & Bard, 2003). Interestingly, the maxilla and mandible are the only bones decorated with multiple "unusually shaped, and much harder white structures," the teeth. The alveolar regions of the maxilla and mandible are also unique and dynamic. They undergo a remodeling process that allows for tooth eruption and biomechanical distribution of occlusal forces throughout the jaw. Also, the alveolar bones are the only bones that physiologically and anatomically connect the external environment to the interior of the body through the periodontium.

2 | JAW BONES DEVELOP SITE-SPECIFIC BONE DISORDERS

Skeletal disorders such as osteoporosis and osteopetrosis affect all bones, but odontogenic tumors, cherubism, and hyperparathyroid jaw tumor syndrome commonly affect jaw bones (Machado et al., 2017; Pepe et al., 2011). Also, fibrous dysplasia affects multiple bone types, but the jaw lesions of fibrous dysplasia display unique radiological and histological patterns that are different from those of axial and appendicular bones (Akintoye et al., 2003). Long bone fibrous dysplasia is radiolucent and displays a haphazard Chinese character trabecular pattern histologically, as opposed to radiopaque maxilla and mandible fibrous dysplasia with less haphazard thin trabeculae (Akintoye et al., 2003). Fibrous dysplasia within the context of the McCune-Albright syndrome is caused by *GNAS* gene mutation of bone mesenchymal stem cells (MSCs) that play vital roles in skeletal homeostasis (Akintoye et al., 2003). As MSCs display phenotypic and functional characteristics that are skeletally site-specific (Akintoye et al., 2006; Matsubara et al., 2005), it is unclear whether skeletal site differences of fibrous dysplasia can be attributed to site specificity of MSCs (Akintoye, Boyce, & Collins, 2013). However, these differential characteristics underscore the distinctive features of the jaw bones.

3 | MESENCHYMAL STEM CELLS ARE SKELETALLY SITE-SPECIFIC

The commitment of MSCs to osteogenic lineage is under the control of transcription factors such as *RUNX2* and *Osterix* and interactions of multiple cytokines and growth factors (Artigas, Urena, Rodriguez-Carballo, Rosa, & Ventura, 2014; Choi et al., 2011). The orofacial MSCs isolated from the maxilla and mandible are skeletally site specific compared to those of the axial and long bones. They are highly proliferative and demonstrate high population doubling and survival properties, and significantly higher *in vitro* and *in vivo* osteogenesis (Akintoye et al., 2006). Orofacial MSCs also enhance systemic immunity compared to non-oral MSCs (Yamaza et al., 2011). These distinctive properties of orofacial MSCs are conserved along the evolutionary line because human, porcine, canine, rat, and mouse MSCs consistently demonstrate skeletal site specificity (Table 1) (Aghaloo et al., 2010; Akintoye et al., 2006; Bugueno, Li, Salat, Qin, & Akintoye, 2017; Dong et al., 2014; Lloyd et al., 2017; Matsubara et al., 2005; Yamaza et al., 2011).

4 | SITE-SPECIFIC AUTOGENOUS MAXILLA AND MANDIBULAR GRAFTS

Trauma, infection, and dental surgery are the major causes of tooth loss and alveolar defects. To restore alveolar defects and missing teeth, a bone graft of adequate MSC quantity and quality may be required to ensure a good prognosis of the final dental restoration. An autogenous bone graft is the gold standard because it produces full graft integration and good functional outcomes. An autogenous graft is osteoconductive, osteoinductive, displays appreciable osteogenesis and graft revascularization, and poses minimal risks of graft rejection. However, a major disadvantage of an autogenous donor graft is the need for a second surgical site and consequent donor site morbidity. Inability to obtain an autogenous graft makes the clinician consider allografts and xenografts, but these are less efficacious and have their own disadvantages. If the site of alveolar bone augmentation is relatively small, an autogenous donor graft is often obtained from another intraoral site such as the maxillary tuberosity, mandibular symphysis, and posterior mandibular regions of the ramus and retromolar area. When it is impracticable to get an appropriate intraoral donor site, extra-oral donor sites such as iliac crest, tibia, fibular, and ribs are often considered. Restoring an alveolar defect with a donor graft from another orofacial bone has proven more successful than from a non-oral bone because the graft resorption rate is one-third slower and implant placement is more successful (Kang et al., 2015; Mertens et al., 2013). Cellular interaction of a donor graft at the recipient site is more effective when bone rich in orofacial MSCs is grafted into the alveolar region, because orofacial MSCs recruit MSCs of similar skeletal site of origin with more affinity than MSCs from non-orofacial sites (Dong et al., 2014). Additionally, orofacial MSCs resist apoptosis associated with surgically induced cellular stress better and attach to titanium with higher affinity to promote cell homing and implant integration. (Akintoye, Giavis, Stefanik, Levin, & Mante, 2008; Dong et al., 2014). Therefore, successful integration of an oral donor graft to the jaw bone can be attributed to distinctive skeletal site-specific proliferative, osteogenic and cell recruitment properties of orofacial MSCs that form the major bulk of the bone marrow cell population within the donor graft.

TABLE 1 Distinctive characteristics of orofacial MSCs compared with long bone MSCs in humans and different animal species

Comparison of orofacial MSCs characteristics with long bone MSCs[a]						
Source of orofacial MSCs	**Mouse (Yamaza et al., 2011)**	**Rat (Aghaloo et al., 2010)**	**Rat (Dong et al., 2014)**	**Canine (Bugueno et al., 2017)**	**Porcine (Lloyd et al., 2017)**	**Human (Akintoye et al., 2006)**
Fold increase relative to long bone MSCs						
Colony forming ability	50	2	2.5	1.5	N/A	2
Proliferative capacity	2	N/A	2	2	2	6
Population doubling capacity	2	N/A	N/A	2	2	4
In vitro osteogenesis	1.5	2.5	2.5	2	3	2
In vivo osteogenesis/ bone regeneration	1.5	4	2	1.5	7	3
Adipogenesis	N/A	N/A	N/A	2	N/A	0.5
Chondrogenesis	N/A	N/A	N/A	2	N/A	N/A
Neurogenesis	N/A	N/A	N/A	Similar	N/A	N/A
Markers of stemness	Similar	N/A	2.5	N/A	N/A	Similar
Recruitment affinity for same skeletal site (orofacial) MSCs	N/A	N/A	6	N/A	N/A	N/A

N/A, not available; MSCs, mesenchymal stem cells.

[a]Summarized from data extracted from the respective reference papers.

5 | SUMMARY

Taken together, the similar embryological origin and superior osteogenesis of orofacial MSCs coupled with enhanced integration of an alveolar donor graft to an alveolar defect underscore the distinctive features of the jaw and alveolar bone regeneration.

CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

Sunday Akintoye conceptualized the idea, obtained the data, and wrote the manuscript.

ORCID

SO Akintoye http://orcid.org/0000-0002-3090-1374

REFERENCES

Aghaloo, T. L., Chaichanasakul, T., Bezouglaia, O., Kang, B., Franco, R., Dry, S. M., … Tetradis, S. (2010). Osteogenic potential of mandibular vs. long-bone marrow stromal cells. *Journal of Dental Research*, *89*, 1293–1298.

Akintoye, S. O., Boyce, A. M., & Collins, M. T. (2013). Dental perspectives in fibrous dysplasia and McCune-Albright syndrome. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *116*, e149–e155.

Akintoye, S. O., Giavis, P., Stefanik, D., Levin, L., & Mante, F. K. (2008). Comparative osteogenesis of maxilla and iliac crest human bone marrow stromal cells attached to oxidized titanium: A pilot study. *Clinical Oral Implants Research*, *19*, 1197–1201.

Akintoye, S. O., Lam, T., Shi, S., Brahim, J., Collins, M. T., & Robey, P. G. (2006). Skeletal site-specific characterization of orofacial and iliac crest human bone marrow stromal cells in same individuals. *Bone*, *38*, 758–768.

Akintoye, S. O., Lee, J. S., Feimster, T., Booher, S., Brahim, J., Kingman, A., … Collins, M. T. (2003). Dental characteristics of fibrous dysplasia and McCune-Albright syndrome. *Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics*, *96*, 275–282.

Artigas, N., Urena, C., Rodriguez-Carballo, E., Rosa, J. L., & Ventura, F. (2014). Mitogen-activated protein kinase (MAPK)-regulated interactions between Osterix and Runx2 are critical for the transcriptional osteogenic program. *Journal of Biological Chemistry*, *289*, 27105–27117.

Bugueno, J., Li, W., Salat, P., Qin, L., & Akintoye, S. O. (2017). The bone regenerative capacity of canine mesenchymal stem cells is regulated by site-specific multilineage differentiation. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *123*, 163–172.

Chai, Y., & Maxson Jr, R. E. (2006). Recent advances in craniofacial morphogenesis. *Developmental Dynamics*, *235*, 2353–2375.

Choi, Y. H., Jeong, H. M., Jin, Y. H., Li, H., Yeo, C. Y., & Lee, K. Y. (2011). Akt phosphorylates and regulates the osteogenic activity of Osterix. *Biochemical and Biophysical Research Communications*, *411*, 637–641.

Cordero, D. R., Brugmann, S., Chu, Y., Bajpai, R., Jame, M., & Helms, J. A. (2011). Cranial neural crest cells on the move: Their roles in craniofacial development. *American Journal of Medical Genetics. Part A*, *155A*, 270–279.

Dong, W., Ge, J., Zhang, P., Fu, Y., Zhang, Z., Cheng, J., & Jiang, H. (2014). Phenotypic characterization of craniofacial bone marrow stromal cells: Unique properties of enhanced osteogenesis, cell recruitment, autophagy, and apoptosis resistance. *Cell and Tissue Research*, *358*, 165–175.

Helms, J. A., & Schneider, R. A. (2003). Cranial skeletal biology. *Nature*, *423*, 326–331.

Kang, Y. H., Kim, H. M., Byun, J. H., Kim, U. K., Sung, I. Y., Cho, Y. C., & Park, B. W. (2015). Stability of simultaneously placed dental implants with autologous bone grafts harvested from the iliac crest or intraoral jaw bone. *BMC Oral Health*, *15*, 172.

Lloyd, B., Tee, B. C., Headley, C., Emam, H., Mallery, S., & Sun, Z. (2017). Similarities and differences between porcine mandibular and limb bone marrow mesenchymal stem cells. *Archives of Oral Biology*, *77*, 1–11.

Machado, R. A., Pontes, H., Pires, F. R., Silveira, H. M., Bufalino, A., Carlos, R., … Fonseca, F. P. (2017). Clinical and genetic analysis of patients with cherubism. *Oral Diseases*, doi: 10.1111/odi.12705. [Epub ahead of print].

Matsubara, T., Suardita, K., Ishii, M., Sugiyama, M., Igarashi, A., Oda, R., … Kato, Y. (2005). Alveolar bone marrow as a cell source for regenerative medicine: Differences between alveolar and iliac bone marrow stromal cells. *Journal of Bone and Mineral Research*, *20*, 399–409.

Mertens, C., Decker, C., Seeberger, R., Hoffmann, J., Sander, A., & Freier, K. (2013). Early bone resorption after vertical bone augmentation–A comparison of calvarial and iliac grafts. *Clinical Oral Implants Research*, *24*, 820–825.

Pepe, J., Cipriani, C., Pilotto, R., De Lucia, F., Castro, C., Lenge, L., … Minisola, S. (2011). Sporadic and hereditary primary hyperparathyroidism. *Journal of Endocrinological Investigation*, *34*, 40–44.

Ramaesh, T., & Bard, J. B. (2003). The growth and morphogenesis of the early mouse mandible: A quantitative analysis. *Journal of Anatomy*, *203*, 213–222.

Yamaza, T., Ren, G., Akiyama, K., Chen, C., Shi, Y., & Shi, S. (2011). Mouse mandible contains distinctive mesenchymal stem cells. *Journal of Dental Research*, *90*, 317–324.

How to cite this article: Akintoye SO. The distinctive jaw and alveolar bone regeneration. *Oral Dis*. 2018;24:49–51. https://doi.org/10.1111/odi.12761