



Review Article

Homeobox genes in teeth development- Short communication

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ARTICLE INFO

Article history:

Received 12-11-2021

Accepted 11-12-2021

Available online 27-01-2022

Keywords:

Homeobox genes

Tooth development

Odontogenesis

Tooth morphogenesis

ABSTRACT

Gene expression controls the cellular differentiation and morphogenesis for body organisation. Every species has different and unique body patterns and this is influenced by certain group of genes called as homeobox genes. Molecular events are involved in the tooth development process or odontogenesis and this is also controlled by homeobox genes. It was first identified in fruit fly *Drosophila Melanogaster*.

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1. Introduction

There are about 180 nucleotide base pairs in homeobox gene and function by producing proteins that bind to the DNA of downstream genes, thereby regulating their expression. It regulates the multiple germ layers to coordinate the cell division and other cellular functions such as cell migration, differentiation, proliferation, and apoptosis through the process of cell-to-cell communication by transcriptional activities of these genes during morphogenesis.^{1,2}

1.1. Classes

There are about two classes of homeobox genes.

1. Class 1 genes are called Hox genes share a high degree of identity in their homeodomain.
2. Class 2 genes share a low degree of identity their homeodomain.³

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1.2. HOX genes

In Hox cluster of genes homeobox sites are first identified. This Hox gene located on the same chromosome, each coding for a particular protein which is regulated by the same cellular mechanisms. Humans contain HOXA, HOXB, HOXC, or HOXD these are 4 clusters of Hox genes found on chromosomes 2, 7, 12, and 17.¹

1.3. Role of muscle segment box (Msx) gene

Msx1 is co-expressed with Msx2 at the site of epithelial - mesenchymal interactions. In dental mesenchyme Msx1 is exclusively expressed whereas both in dental epithelium and in mesenchyme Msx2 is expressed but at first it is expressed in mesenchyme. Msx has increased expression in cap stage. Msx1 expressed in enamel knot, inner enamel epithelium and dental papilla whereas Msx2 expressed in odontoblasts, cuspal formation, root initiation.^{3,4}

1.4. Role of paired box (Pax) gene

It is the earliest mesenchymal gene. This gene localizes at the site of tooth bud. Regulators of organogenesis, maintains

pleuripotency of stem cell. Non syndrome oligodontia is associated with mutations in exon 1, 2 and 4 mostly in exon 2. Frame shift mutation causing premature termination of translation according to Stockton mutation in the Pax9 gene.^{1,3}

1.5. Role of pitx gene

Before odontogenesis, pitx gene is expressed early in distal and proximal stomodeal ectoderm of both maxillary and mandibular processes. Pitx2 expression is seen in the dental epithelium during tooth formation. In the developing molars & incisors of the mandible, Pitx1 gene is expressed in both the epithelium and in the mesenchyme. In the proximal mesenchyme of the mandible Pitx1 is expressed first before the placode stage.⁴

1.6. Role of distal less box (Dlx) gene

This gene is expressed both in epithelium & in mesenchyme. In epithelium of bud stage Dlx2, Dlx3 are expressed which helps in ameloblastic differentiation and amelogenesis. Dlx-1 is seen exclusively in dental mesenchyme whereas Dlx-2 present in both the epithelium & in mesenchyme. In cap stage Dlx-1 is expressed & in early bell stage Dlx6 is expressed. In cervical loop Dlx5 is expressed. The roles of Dlx4 and Dlx6 have not been extensively studied.^{3,4}

1.7. Role of lymphoid enhancing factors (Lef-1) gene

LEF1 gene is accountable for an instantaneous regulation of Fgf4 expression to relay a Wnt signal to a cascade of FGF signalling activities that mediate the serial and reciprocal interactions between the dental epithelial cells and also the CNC-derived dental mesenchyme throughout tooth development. This gene involved in Wnt signalling pathway and it express in condensing mesenchyme in bud stage & adjacent basal cells of epithelium. For initiation & cytodifferentiation this gene is essential.^{3,5}

1.8. Role of lim homeobox domain (Lhx) gene

Lhx6 and Lhx7 are the earliest mesenchymal markers of tooth development. They are expressed within the ectomesenchyme with Lhx6 restricted to the proximal components of upper jaw and submaxilla whereas Lhx7 expressed throughout the proximal-distal axis of each maxilla and mandible. Lhx6 and Lhx8 genes are expressed in both maxillary and mandibular process and are seen in mesenchyme of developing molars. In developing incisors, Isl1 (Islet-1) gene is expressed. This is another member of Lim gene family.²⁻⁴

1.9. Role of RUNX-2, OSX, and DSPP in tooth development

For odontoblast and osteoblast differentiation RUNX-2 transcription factor is essential. In mice it shows odontogenesis progress only up to cap or early bell stage when there is a deficient RUNX-2. In humans it shows enamel hypoplasia, abnormal tooth eruption and supernumerary teeth during mutation of RUNX-2 gene.

It is an osteoblast specific transcription factor. In mesenchymal cells of the tooth germ Osterix (Osx) is expressed. In the cascade of osteoblast differentiation signalling pathway, Osx acts as a downstream gene of Runx-2.

In the later stage of tooth development very high expression of Dspp mRNA expression is seen in odontoblast.⁶

1.10. Role of sonic hedge hog (Shh) and Glioma homologue (Gli) genes

Shh gene is expressed in Bud and cap stages of tooth development and also in Hertwig's epithelial root sheath for root formation. Gli1 and Gli2 helps in Shh expression. Shh in promoting morphogenetic movement within the early tooth bud through cell polarization, influencing each cuspal growth and root development throughout the later stages of development, and within the mature dentition it plays a crucial role in defining tooth number.^{3,7}

1.11. Role of bone morphogenic protein (BMP)

The BMPs induce bone formation in vitro and in vivo and it is a homodimeric proteins. It consists of eight members, who based upon amino acid similarity are divided into three subclasses. In the developing molar tooth germ, BMP heterodimers such as BMP-2, BMP-4, and BMP-7 mRNA are up-regulated whereas in both dental epithelium as well as dental mesenchyme BMP-4 and BMP-7 are expressed which leads to complication.⁶

1.12. Role of other homeobox genes

In the proximal mesenchyme of the mandibular and maxillary processes Barx1 is expressed and it is maintained in dental mesenchyme of all molars.⁸

In the distal mesenchyme of the mandibular component of the first branchial arch T-cell leukaemia homeobox containing gene Tlx1 is expressed before appearing in the dental epithelium at the site where lower incisors will form. In the dental epithelium of mandibular incisors Tlx1 expression is restricted.⁹

In the dental epithelium of all developing teeth from the placode to the cap stage Irx1 homeobox transcription factors is expressed. For tooth morphogenesis this Irx1 is not required.¹⁰

1.13. Control of tooth germ position

To specify the sites of tooth initiation, Fibroblast growth factor - 8 (Fgf-8) has been proposed to work antagonistically with Bone morphogenetic protein - 4 (Bmp-4). It is also shown that epithelial Bmp-4 and mesenchymal Bmp-2 antagonise the induction of mesenchymal Pax -9 by Fgf-8.

Close interactions are seen between Bmp-4 & Fgf-8 with each other. Another possible regulator is Pitx-2 for Fgf-8 whose epithelial expression prefigures the location of teeth. Beyond epithelial thickening or bud stage Pitx-2 has been shown to be required. Pitx-2 seems to regulate Bmp-4 in a negative feedback mechanism while Fgf-8 in a positive feedback mechanism.³

1.14. Models for tooth type determination

1.15. Field model

Dahlberg adapted Butler's concepts to the human dentition and suggested that there is a field of influence that acts on each of the tooth classes like incisors, canines, premolars and molars. This model says that, within the ectomesenchyme the factors responsible for tooth shape resides in distinct graded and overlapping fields for each tooth family. The fact that each of the fields expresses different combinations of patterning homeobox genes supports this theory.

1.16. Clone model

Osborn suggested that a single clone of pre-programmed cells resulted in the development of all teeth within a given class. This model says that, by the programming of epithelium each tooth is derived from a clone of ectomesenchymal cells to produce a given pattern. For example, it has been postulated that a molar clone of cells stimulates the dental lamina to initiate molar development.^{3,11}

2. Conclusion

Homeobox genes are responsible for molecular events seen in patterning of the dentition and in tooth morphogenesis. During odontogenesis, any mutation seen in these homeobox genes will result in developmental disturbances. These genes are also responsible for the other ectodermal appendages like nail, hair follicle and mammary gland development. Thus, understanding the complete molecular events and signalling mechanism by homeobox genes in odontogenesis, it gives good scope in research fields and gene targeted therapy in future.

3. Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

4. Source of Funding

None.

References

1. Suryadeva S, Khan MB. Role of homeobox genes in tooth morphogenesis: A review. *J Clin Diagn Res: JCDR*. 2015;9(2):9–12. doi:10.7860/JCDR/2015/11067.5606.
2. Ramanathan A, Srija TC, Sukumaran P, Zain RB, Kasim NH. Homeobox genes and tooth development: understanding the biological pathways and applications in regenerative dental science. *Arch Oral Biol*. 2018;85:23–39. doi:10.1016/j.archoralbio.2017.09.033.
3. Rinky A, Ankit A, Manisha T, Shweta C. Homeobox Genes-The Mirror of Tooth Development. *Indian J Dent Adv*. 2013;5(3):1291–3.
4. Duverger O, Morasso MI. Role of homeobox genes in the patterning, specification, and differentiation of ectodermal appendages in mammals. *J Cellular Physiology*. 2008;216(2):337–46. doi:10.1002/jcp.21491.
5. Sasaki T, Ito Y, Xu X, Han J, Bringas P, Maeda T, et al. LEF1 is a critical epithelial survival factor during tooth morphogenesis. *Dev Biol*. 2005;278(1):130–43.
6. Doshi R, Kulkarni U, Shinde S, Sabane A, Patil A. Role of genes in odontogenesis. *Br J Med Med Res*. 2016;14(6):1–9.
7. Seppala M, Fraser GJ, Birjandi AA, Xavier GM, Cobourne MT. Sonic hedgehog signaling and development of the dentition. *J Dev Biol*. 2017;5(2):6. doi:10.3390/jdb5020006.
8. Tissier-Seta JP, Mucchielli ML, Mark M, Mattei MG, Goridis C, Brunet JF, et al. Barx1, a new mouse homeodomain transcription factor expressed in cranio-facial ectomesenchyme and the stomach. *Mech Dev*. 1995;51(1):3–15. doi:10.1016/0925-4773(94)00343-1.
9. Raju K, Tang S, Dubé ID, Kamel-Reid S, Bryce DM, Breitman ML. Characterization and developmental expression of Tlx-1, the murine homolog of HOX11. *Mech Dev*. 1993;44(1):51–64. doi:10.1016/0925-4773(93)90016-q.
10. Ferguson CA, Tucker AS, Heikinheimo K, Nomura M, Oh P, Li E, et al. The role of effectors of the activin signalling pathway, activin receptors IIA and IIB, and Smad2, in patterning of tooth development. *Development*. 2021;128(22):4605–13.
11. Townsend G, Harris EF, Lesot H, Clauss F, Brook A. Morphogenetic fields within the human dentition: a new, clinically relevant synthesis of an old concept. *Arch Oral Biol*. 2009;54(1):34–44.

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Cite this article: Jothy Arvind A V, Muthanandam S, Devy AS, Vidyalakshmi S. Homeobox genes in teeth development- Short communication. *International Dental Journal of Student's Research* 2021;9(4):181-183.