Mechanism of Patterning of Dentition: A Review

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Abstract
Patterning of dentition means the determination of tooth types at their correct positions in the jaws. This is a complex process for which various theories have been proposed. Recent studies showed that this process involves expression of various genes. This article presents a systematic review on patterning of dentition.
Key words: patterning, dentition, field theory, clonal theory, homeobox genes, msx, dlx, activin.

Introduction

The determination of specific tooth types at their correct positions in the jaws is referred to as patterning of the dentition. The determination of crown process is a remarkably consistent process. Although in some animals teeth are all of the same shape (homodont), in most mammals they are different (heterodont), falling into three families: incisiform, caniniform and molariform. The patterning is tightly controlled: transpositions are occasionally seen, but they usually involve teeth at the border of a particular series (i.e. canines and premolars) and more severe anomalies of patterning (i.e. molars developing at the front of the arch) do not occur.[1]

Classically two theories have been proposed to account for this.

The field theory (Butler, 1939): This theory suggests that all tooth primordia are initially equivalent, with the individual shape that they subsequently develop into being controlled by varying concentration of morphogens in the local environment. A number of diffusible signaling molecules have been identified that may be involved in concentration-dependant, threshold response mechanisms which would produce periodicity along the developing dental axis. However, if these mechanisms are responsible for patterning in both dentition, then they must act very early on in the development process. Unlike the mandibular dental axis the developing maxillary dentition is not continuous. The maxillary incisors develop in the medial nasal processes, whilst the remainder of the dentition develops in the maxillary process of the first arch.[2]

Clonal model (Osborn, 1978): In this model, the tooth primordial are said to be prespecified with each migrating cell population being equipped with the necessary positional information to produce different classes of teeth from inception. Migration of the neural crest cells from the region of the developing hindbrain provides much of the mesenchyme of the developing orofacial region; including that contributing to odontogenesis.[3] Histological data of discrete initiation favor the clone model rather than the field model of a diffusible morphogen. However, Westgaard and Ferguson have proposed a hybrid 'progress zone model' where the progressive disto-proximal restriction of Hox-8 expression in epithelium and mesenchyme coincides with this model.[1]

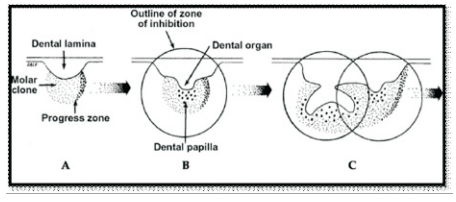

Fig 1: Clone theory:[3]
A) The molar clone ectomesenchyme has

induced the dental lamina to begin tooth development. The clone and dental lamina progress posteriorly.

B) When a clone reaches the critical size, a tooth bud is initiated at its centre,

C) The next tooth bud is not initiated unless the progress zone of the clone escapes the influence of a zone of inhibition surrounding the tooth bud

The homeobox code model for dental patterning is based on observations of the spatially restricted expression of several homeobox genes in the jaw primordial ectomesenchyme cells before E11. The early expression of Msx-1 and Msx-2 homeobox genes before the initiation of tooth germs is restricted to distal, midline ectomesenchyme in regions where incisors and canines but not multicuspid teeth develop; whereas Dlx-1 and Dlx-2 are expressed in ectomesenchyme cells where multicuspid teeth, but not incisors or canines develop. These expression domains are broad and do not exactly correspond to specific tooth types. Rather they are considered to define broad territories.[1]

Expression of Barx-1 overlaps with Dlx-1 and Dlx-2 and corresponds closely to ectomesenchyaml cells that develop into molars. The homeobox code model proposes that the overlapping domains of these genes provide the positional information for tooth type determination. Support for this model comes from the dental phenotype of Dlx-1$^{-/-}$ and Dlx-2$^{-/-}$ double knockout mice in which development of maxillary molar teeth is arrested in epithelial thickening stage. As predicted by this model, incisor development is normal in these mice. Further support for this model comes from misexpression of Barx-1 in distal ectomesenchyme cells, which results in incisor tooth germs developing as molars. FGF-8 in proximal ectoderm induces Barx-1 expression whereas Bmp-4 in the distal ectoderm represses Barx-1 expression. Experimentally induced expression of barx-1 in distal ectomesenchyme by inhibition of BMP signaling has the effect of repressing Msx gene expression, which is induced in distal mesenchyme by BMP-4.[1]

There are three different conclusions from this model. The first is that there is no one specific gene for each tooth type. Second, the code is both positive and negative; thus the absence of a gene is as important as its presence. Third, the code is overlapping and can thus provide morphogenetic cues for many different tooth shapes.[4]

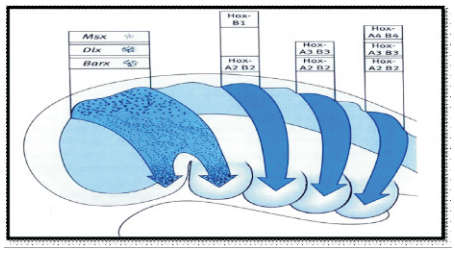

Fig 2: Migrating neural crest cells express the same homeobox (Hox) genes as their precursors in the rhombomeres from which they derive. Note that Hox genes are not expressed anterior to rhombomere 3. A new set of patterning genes (Msx, Dlx, Barx) has evolved to bring about development of cephalic structures so that a "Hox code" also is transferred to the brachial arches and developing face.[1]

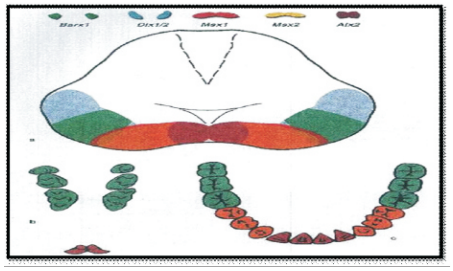

Fig 3: Homeobox code model for dental patterning.[1]

A. Domains of Barx-1 and Dlx-1/-2 expression overlap in the mesenchyme of the presumptive molar region, whereas domains of Msx-1, Msx-2 and Alx-3 overlap in presumptive incisor mesenchyme.

B. Mouse dental pattern. Incisors deriving from MSX-1/Alx-3 expressing cells, molars deriving from Barx-1/Dlx-1/ Dlx-2 expressing cells

C. Human dental pattern. Premolars and canines can be derived from the same odontogenic code as that observed in mice by virtue of the overlapping domains of gene expression. Thus canines and premolars may be derived from cells expressing Dlx-1/-2 and Msx-1, for example.

An obvious question therefore is how are highly restricted domains of ectomesenchymal gene expression regulated? Two possible mechanisms are that: (1) neural crest cells contain a pre pattern and (2) neural crest cells respond to positional signals from the oral epithelium. Removal of epithelium from mandibular arches at E10 or before, results in a total and rapid loss of almost all ectomesenchymal homeobox gene expression. Removal of epithelium at E10.5 also results in loss of gene expression and subsequent addition of FGF8 beads restores expression in the original expression domains only. Removal of epithelium at E11 does not affect gene expression, indicating that the spatial homeobox expression domains are established and maintained in the absence of epithelial signals.[5]

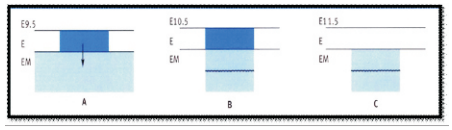

Fig 4: Schematic representation explains the signaling interdependence between epithelium (E) and ectomesenchyme (EM).[5]

A. The uncommitted mesenchyme cells equally responsive and dependand on epithelium for signals.

B. The domains of ectomesenchymal gene expression become fixed but still dependant on epithelium for signals.

C. The fixed gene expression domains of the ectomesenchyme are no more dependent on epithelium.

Up to E10, all ectomesenchyme cells appear to be uncommitted and competent to respond to epithelial signals regardless of position. By E10.5, the spatial expression domains have been established in the ectomesenchyme by the action of epithelial signals such as FGF8 and BMP4. By E11, expression of spatial ectomesenchymal genes does not require epithelial signals. Epithelial signals thus regulate the spatial expression of homeobox genes in the ectomesenchyme which in turn control morphogenetic pathways, probably by influencing enamel knot function. The control of tooth shape thus mirrors the general control of tooth formation, with information being passed from epithelium to ectomesenchyme and back again to epithelium.[6] Recombination experiments have revealed much important information about the rostrocaudal positioning of tooth and arch patterning.

1. Primarily it is that the first brachial arch epithelium is unique in containing instructive signals for odontogenesis and these can over-ride the pre-patterning information present in the neural crest cells.
2. The maxillary and mandibular epithelia are interchangeable as regulators of ectomesenchymal gene expression. If this is true, then the instructive signals must produce identical differentiation pathways which are not the case, as it is obvious that different skeletal structures and subtly

different teeth are produced in spite of being covered by same epithelium.[5]

Functional redundancy and their complexities: Despite both the genes being expressed in identical patterns on the proximal maxilla and mandibular primordia, the normal development of mandibular molars and the failure of maxillary molars to develop in Dlx1/2 double mutants indicate a basic genetic difference between the specification of molar morphogenesis during development of upper and lower jaws. Dlx5 and Dlx6 are co-expressed in proximal ectomesenchyme of mandibular primordial in domains similar to Dlx1 and Dlx2. Significantly however Dlx5 and Dlx6 are not expressed in the maxillary arch. Mutations in Dlx1 and/or DLx2 affect maxilla development, presumably because Dlx5 and Dlx6 genes carry out this function in the mandible in the absence of Dlx1 and Dlx2.[6]

The activin enigma: Activin is a member of the TGFβ family of growth factors. Activin proteins function as dimmers consisting of βA and βB subunits encoded respectively by activin βA and activin βB genes. Activin βA expression is localized in presumptive tooth mesenchyme of all teeth, where it acts as an early mesenchymal to epithelial signal. Surprisingly mouse mutants for activin βA lack all teeth except the maxillary molars. This phenotype is reciprocal of Dlx1/2 phenotype. The Dlx1/2 phenotype can be explained by functional redundancy with other Dlx genes, whereas the activin βA phenotype cannot be explained by redundancy, since activin βA/βB double mutants have the same phenotype as activin βA single mutants.[7]

The most obvious explanation for the development of maxillary molars in the absence of activin is that the role of activin in these teeth is carried out by another TGFβ family ligand, binding to activin receptor and stimulating the same pathway. This seems not to be the case, since the expression of activin signaling target genes, such as follistatin, is lost in the maxillary molar tooth germs in activin βA mutants. The molecular basis of this phenotype is yet to be explained.[6]

References

1. Nanci A. Ten Cate's Oral histology, development, structure and function. 7th edition. Elsevier Publication; 2008.p.34-46, 79-95, 147-178.
2. Cobourne TM. The genetic control of early odontogenesis. British J Orthodontics 1999;26:21-28.
3. Chaterjee S, Boaz K. Molecular biology of odontogenesis. J Orofacial Sciences 2011;3(1):57-61.
4. Sharpe TS. Neural crest and tooth morphogenesis. Adv Dent Res 2001;15:4-7.
5. Kumar GS. Orban's Oral histology and embryology. 13th edition. Elsevier: 2007.p.27-35, 37-38, 142, 332-345.
6. Garant PR. Oral cells and tissues. Quintessence Publishing Co. 2003.p.1-19.
7. Miletich I, Sharpe TP. Normal and abnormal dental development. Human Molecular Genetics 2003;12(1):69-73.