MEDICAL JOURNAL ARMED FORCES INDIA XXX (2016) XXX–XXX

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/mjafi

Review Article

Mapping the milestones in tooth regeneration: Current trends and future research

Atanu Bhanja [a,*], Col D.S.J. D'Souza (Retd) [b]

[a] Assistant Professor, Dept of Dental Surgery, Sikkim Manipal Institute of Medical Sciences, Gangtok, India
[b] Professor & HOD, Dept of Dental Surgery, Sikkim Manipal Institute of Medical Sciences, Gangtok, India

ARTICLE INFO

Article history:
Received 26 February 2016
Accepted 10 May 2016
Available online xxx

Keywords:
Odontogenesis
Regeneration
Stem cells
Tissue engineering
Tooth

ABSTRACT

Research into finding the perfect replacement for lost dentition is an ever-evolving and rapidly advancing subject involving many scientific disciplines. The present consensus appears to be that regeneration of tooth in morphological and functional form is the ideal answer to lost tooth replacement. This article traces the milestones in this elusive search for the ultimate tooth replacement. The various research developments are highlighted that are aimed at the final goal of being able to ''re-grow a natural tooth''. Whole tooth regeneration is technically challenging and further research into this field of complex molecular biology, embryology, biomaterials and stem cells is required to answer the unsolved questions. However, the milestones that have been crossed in the attempts at whole tooth regeneration have been remarkable and the future is quite promising. This article highlights the noteworthy research work that is being done in the field of whole tooth regeneration with a view to not only inform the clinicians of the significant developments but also inspire them to actively participate in this rapidly evolving field.

Introduction

Regeneration of lost tissue or organs for rehabilitation of patients has been the ultimate dream of every clinician and healthcare researcher. Due to the unique, multifarious role of the teeth and associated structures there has been a sustained effort to replace the missing dentition over many centuries. From the prehistoric attempts of wiring together extracted teeth, various denture designs and materials to the development of dental implants the search has had many unique breakthroughs and path-breaking developments. Despite all its advantages, dental implants (currently considered to be the best alternative) have certain inherent drawbacks. They lack the 3-dimensional structure of natural teeth and consequently their functionality, such as a periodontal ligament which gives a sense of proprioception and cushioning effect; pulpal tissue that act as a reparative source of cells and the lack of thermal stimuli through nerve endings' that all of which have got a protective role teleologically.

The consensus, therefore, has been that regeneration of tooth in morphological and functional form is the only perfect

* *Corresponding author*. Tel.: +91 9434142646.
E-mail address: doc.abhanja@gmail.com (A. Bhanja).
http://dx.doi.org/10.1016/j.mjafi.2016.05.004

answer to lost tooth replacement. This article traces the milestones in this elusive search for the ultimate tooth replacement. We attempt to highlight the various research developments that are aimed at the final goal of being able to ''re-grow a natural tooth''. This article highlights the noteworthy research work that is being done in the field of whole tooth regeneration with a view to not only inform the clinicians of the significant developments but also inspire them to actively participate in this rapidly evolving field.

Background

To understand the models of whole tooth regeneration, we need to appreciate certain concepts of evolutionary biology and embryology. These biological processes may be replicated in the laboratory via tissue engineering process using stem cells.

Evolutionary biology

As we move up the evolutionary chain from fish to reptiles to mammals, we see that the following characteristics are observed: the total number of teeth decrease (from polyodonty to oligodonty); morphological complexity increases (from homodonty to heterodonty) and tooth regeneration capability also decreases (from polyphyodonty to di- and/or monophyodonty).[1] Many non-mammalian vertebrates are polyphyodonts and have cyclical rounds of tooth regeneration throughout life e.g. – in an adult cichlid fish each tooth is replaced every 30–100 days. However, most mammals like humans are diphyodont and gets only two sets of teeth in a life span. In contrast, mice have one set of dentition which comprises one incisor and three molars in a single row in each quadrant of the jaw. These incisors have a self-renewal capacity with the continuous deposition of enamel labially. This self-renewal or self-regenerative ability of tooth is due to presence of stem cells in post-embryonic tissues.[2]

Many explanations have been postulated of the manner in which the evolutionary process has made its imprint into the biomolecular level, for evolving vertebrates from polyphyodonty to di- and/or monophyodonty. This may be via, a change in genetic expression, followed by modification in post-transcription and translational pathway leading to modification of signaling.[3]

Embryology and signaling

Not only are the teeth functionally and morphologically unique in the human body, but even the process of odontogenesis is remarkable in the sense of its functional outcome i.e. the teeth are region-specific (incisor and canines in anterior to premolars and molars in posterior regions of the jaws). The stages of tooth development have been classically described, from early to late as: Lamina, Bud, Cap and Bell stages (early and late stage), by the morphologic changes which are discernible under the microscope.[4]

In recent years, with a better understanding of molecular control, the process of odontogenesis can be broadly described as three closely-linked processes – initiation, patterning and morphogenesis which are all integrally associated with sequential differentiation. All these stages are controlled by highly complicated, sequential mutual interactions between two major cell types: stomodeal ectoderm and ectomesenchyme (derived from neural crest cells). These mutual interactions are regulated by growth factors, transcription factors (approx. 100) and odontogenic genes (approx. 300). The site of tooth formation, morphological differences (incisor or molar) and other phenotypical characteristics are controlled by different spatiotemporal expression of odontogenic genes.[1,5]

Initiation of teeth and determination of position

All teeth, including supernumeraries, develop only in the dental lamina. Initially FGF8 (Fibroblast Growth Factor) activity in the presumptive dental epithelium determines the oral–aboral axis of 1st branchial arch. Later, FGF & BMP (Bone Morphogenetic Protein) signaling in epithelium determine the tooth-forming site by regulating genetic expression of signaling molecules such as *Pax9* in mesenchyme & *Pitx2* in dental lamina.[5] Studies, indicate *Wingless* (*Wnt*) and *Sonic hedgehog signaling* (*Shh*) pathway also play a role in positional specification. Initially *Shh* is only expressed at regions where the tooth formation is desirable, while *Wnt7b* is expressed in the other areas of the oral epithelium. Ectopic expression of *Wnt7b* in dental epithelium represses Shh signaling, leading to inhibition of tooth formation. This highly coordinated genetic interaction helps to limit the tooth formation to specific regions in the jaws.[6]

Tooth identity or patterning

Tissue recombination experiments have confirmed that early information for patterning of tooth identity (incisor vs molar) remains in the presumptive dental epithelium even before neural crest-derived cells migrate to the branchial arch. Again FGF8 and BMP4 are master molecules in induction of the earliest patterning information in the ectomesenchyme by a spatial pattern of genetic expression called 'odontogenic homeobox code'.[5,7] This odontogenic homeobox code basically consists of a specific combination of homeobox genes in the ectomesenchyme that determines type and shape of teeth. Expression of *Dlx and Barx1* in ectomesenchyme are specific for molar teeth pattern, whereas *Msx1*, *Msx2* are determinants for incisor formation.[8]

Tooth morphogenesis

The determination of tooth-crown shape occurs at the time of bud stage. The 'odontogenic homeobox code' specifies tooth crown shape and regulates epithelial folding at the transition of Bud to Cap stage. The transition from Bud to Cap stage is one of the most critical steps in morphogenesis – when the enamel knot forms in dental epithelium and acts as a signaling center for control of crown shape. Nearly 10 signaling molecules belonging to *BMP*, *FGF*, *Wnt* and *Shh* families, are expressed in