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Review paper

Making Sense of Orthodontic Genetics: A Simplified Conceptual Overview

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ARTICLE INFO	ABSTRACT
	In oral cavity, disturbances due to genetic alterations may range from lack of tooth development to morphological defects. Due to technical advances in genetic engineering and molecular biology, valuable information regarding dentofacial growth could be studied in detailed manner. This helps us to explain the aetiology and pathogenesis of many dentofacial disorders. The success in treatment lies first in determining the aetiology of tooth anomalies and finally differentiating the effect of genes and environment on the orofacial diseases of that particular individual. Types of Genetic Factors influence numerous biological processes including orthodontic tooth movement (OTM), external apical root resorption, and problems with tooth formation and/or eruption. Therefore, when a clinician has a good understanding of the genetic factors that influence OTM and some of the genetically influenced problems associated with OTM, treatment outcomes can be improved for many of their patients.

1. Introduction

Body organisation requires cell differentiation and morphogenesis which are controlled by gene expression. Gene expression is defined as an activation of a gene that results in production of polypeptide/ protein that can activate/deactivate other genes with the influence of transcription factors (growth factors)(Suryadeva & Khan, 2015). Every organism has a unique body pattern because of the influence of Homeobox genes. These seem to be the master genes that help in development of individual structures from different areas of the body (Suryadeva & Khan, (2015). They are likely to be an important fundamental in evolution of the specialized body parts of many animal species and the differences

between different organisms can be due to different modes of action of homeobox genes. A homeobox is a DNA sequence found within genes that are involved in the regulation of patterns of anatomical development (morphogenesis) in human beings (Hughes & Kaufman, 2002). The homeobox is about 180 base pairs long. It encodes a protein domain (homeodomain) which helps in binding with the DNA. The homeodomain is capable of recognizing and binding to specific DNA sequences (Schindler, Beckmann et.al, 1993). During embryogenesis, through the early recognition property of the homeodomain, the homeoproteins are believed to regulate the entire expression of genes and also direct

the formation of many body structures (Suryadeva & Khan, 2015) . Homeobox genes encode transcription factors that can regulate expression of other genes. This domain is first identified in Drosophila (fruit fly) (Mark, Rijli et. al, 1997). A genetic factor can be defined as a gene or a specific gene variation that has an effect on some characteristic(s) of an individual or their offspring, where a gene is the smallest unit of inherited information (Morgan, 1917) . Inherited and newly introduced (sporadic) gene variations may be defined simply as a single nucleotide change at a specific location in the DNA code (i.e., a polymorphism), or they could consist of deletions, insertions, amplifications/duplications, inversions, and/or transposition of larger portions of the DNA code.

2. Discussion

2.1 Gene Responsible for Craniofacial Defect

Attimesit becomesdifficultfor a cliniciantodetermine the cause of a disease, especially if the disease isheritable and its symptoms are a part of the presentation put forward by genetically determined traits of a disorder (Morgan, 1997). The presence of many affected members in a family suggests its genetic etiology. However, to determine that a disease has a definite genetic basis, it should exhibit a specific pattern of inheritance (dominant, recessive or X-linked, etc.)(Mahdieh & Rabbani, 2013). When the gene responsible for disease is transmitted from one generation to the next. It follows specific laws of mendelian inheritance (Alcaïs, Quintana-Murc et. al, 2010). Though this is true for the diseases which are due to single gene (monogenic) defects. Genetic diseases are also determined due to the action of many genes (polygenic) acting together. Not only this, some diseases are originated out of interactions between many genes and environmental factors (multifactorial).

2.2 Etiology of Tooth Agenesis

Though many environmental etiological factors for tooth agenesis have been identified. There is definitive proof that genetic factors play a major role in their etiology (Pal & Mahato, 2010). Environmental factors that are implicated are maternal systemic diseases (maternal diabetes, hypothyroidism, rubella infection during pregnancy), anticancer treatment during childhood (radiotherapy and chemotherapy) (Pal & Mahato, 2010).

2.3 Genetics of Tooth Agenesis

Pax-9 and Msx-1 are two key genes involved in the embryological development of teeth and their mutation leads to tooth agenesi. Pax-9 is situated on chromosome (14q21) and belongs to the Pax gene family that encodes a group of transcription factors playing a major role in early development (Satokata & Maas, 1994). Pax proteins are defined by the presence of a DNA-binding domain, the 'paired domain', which makes sequence-specific contact with the target DNA region. Msx1 is a homeobox gene involved in numerous epithelialmesenchymal interactions during vertebrate embryogenesis and appears to be incredibly significant during early tooth development. Pax-9 and Msx-1 encodes transcription factors that are known to be essential for the switch in the odontogenic potential of developing tissues in the epithelium and the mesenchyme. These molecules play an important role in the maintenance of mesenchymal Bmp4 expression responsible for the formation of the dental organ. Pax-9 is able to regulate Msx-1 expression directly and interact with Msx-1 at the protein level to enhance its ability to transactive Msx-1 and Bmp4 expression during tooth development. Pax-9 and Msx1 act as partners in a signaling pathway that involves Bmp4. Furthermore, the regulation of Bmp4 expression by the interaction of Pax-9 with Msx-1 at the level of transcription and through formation of a protein complex determines the fate of the transition from the bud to cap stage during tooth development (Satokata &, Maas, 1994). Till date seven Msx-1 mutations as well as some whole gene deletions have been discovered in tooth agenesis patients. Msx-1 frameshift mutation is responsible for autosomal-dominant oligodontia without clefting or nail dysplasia. The mutation involves duplication of the guanine nucleotide at position 62 in exon 1 of the Msx-1 gene. This mutation in Msx1 is usually associated with the absence of multiple permanent teeth including all second bicuspids and mandibular central incisors (Satokata &, Maas, 1994). A number of mutations (upto 15) have been identified in the Pax genes that include nonsense, missense, frameshift and deletion types of defects. Mutation in the initiation codon of Pax-9 causes severe or complete inhibition of Pax9 translation at one allele resulting in a reduced amount

of Pax-9 transcription factor, representing a haploinsufficiency for Pax-9. This functional insufficiency or absence of Pax-9 protein produced from Pax9 gene ultimately results in tooth agenesis. The Msx1 and Pax9 kindred's have a high but equal probability of missing the third molars and hence the absence of third molars is not a useful indicator of the particular gene (Msx1 or Pax9) that is likely to be affected in a given kindred. Mutations in Msx1 and Pax-9 genes may cause different types of oligodontia (different sets of teeth are missing in different gene mutations). For example all individuals with a mutation in Msx-1 lack all second premolars and third molars (and a variable number of other permanent teeth). Typically, mutations in the Pax-9 cause agenesis of most permanent molars (and again, a variable number of other permanent teeth). These differences presumably reflect different functions of these genes during development. Very recently it has been shown that oligodontia and predisposition to cancer are caused by a nonsense mutation in the Axin-2 gene. The Axin-2 is a Wnt-signaling regulator. Wnt signaling regulates embryonic pattern formation and morphogenesis of most of the organs. Wnt-signal activity is necessary for normal tooth development. During tooth development Axin2 is expressed in the dental mesenchyme, the odontoblasts and the enamel knot. Aberrations of regulation of Wnt signaling may lead to cancer. The nonsense mutation of Axin2 is not only associated with tooth agenesis but also with colorectal cancer (Satokata &, Maas, 1994). Dlx1 and Dlx2 genes play an important role in odontogenic patterning. These genes are important in the development of maxillary molars in mice. But these genes are not required for development of incisors and mandibular molars. The mutation of Dlx1 and Dlx2 in mice leads to failure of development of maxillary molars.

2.4 Genes Responsible for Tooth Patterning and Development

Information regarding tooth organogenesis was found by doing number of trails on mouse embryos as experimental material)(Suryadeva & Khan, 2015). All these studies show that there is a direct genetic control on odontogenesis, which determines the position, number, size and shape of the teeth18. Tooth formation undergoes different stages like bud, cap and bell stage during its developmental process. During the bell stage cytodifferentiation occurs which lead to the formation of enamel, dentin, Periodontal ligament which is a supporting structure of the tooth (Tucker & Sharpe, 1999). Like other development processes during the embryonic phase morpho differentiation of teeth occurs under the influence of first branchial arch, where complex interactions between the stomodeal epithelium which is ectodermal derivative and the underlying mesenchyme which cranial neural crest derivative take place. More than 300 genes are involved in this processes and prominent role is played by the transcription factors that have a homeodomain. The homeodomain consists of 60 aminoacids with a helix-turnhelix DNA binding protein and is encoded by a homeobox sequence (Satokata &, Maas, 1994). Not only homeodomain facilitates it binding with DNA but transcription factors also contain a transactivation domain that interacts with a RNA polymerase and these transcription factors are in turn involved in the regulation of homeobox gene expression sites thus having a role in activation of genes in embryogenesis.

Genes Responsible For Orthodontic Tooth Movement

As orthodontic force is placed on the teeth and the neighboring periodontal ligament (PDL) is compressed, the immune system responds at the site to relieve the tissue stress. As part of the stress response, ATP is released from platelets and can bind to the P2RX7 membrane channel protein located on the surface of immune cells and/or cells of the PDL (Cakan, Ulkur et. al, 2013). Upon binding ATP, the P2RX7 ion channel is opened, allowing the exchange of intracellular potassium (K +) and extracellular sodium (Na++), along with triggering the elevation of calcium (Ca++) from intracellular stores. Elevation of intracellular Ca ++ will activate caspase-1 (also termed IL-1β converting enzyme or ICE) which is located in inflame some complexes with the cell Caspase-1 cleaves the pro-IL-1β molecule, releasing active mature IL-1β for biological function (Nishijima, Yamaguchi et. al, 2006). IL-1β can recruit other inflammatory cells to the site of tissue damage, and it can bind to its receptor on the surface of pro-osteoblastic cells in order to signal the activation of such genes as RANKL and OPG . When RANKL protein is synthesized and expressed on the surface of the osteoblastic cells, in concert with the production of MCSF and its binding to the c-fms receptor on the surface of pre-osteoclastic cells, the osteoclast precursor cells are signaled to mature into functional osteoclasts. OPG and soluble RANKL (sRANKL) can act

to dampen the maturation signal to pro-osteoclast cells by interfering with RANKL: RANK interactions. The action of both osteoblasts and osteoclasts is needed to resolve the tissue stresses within the PDL from orthodontic force application.

2.5 Crispr The Furutre of Genetic Disease Medicine

Clustered regularly interspaced short palindromic repeats. It means repetitive DNA sequence. It is a genetic engineering technique in molecular biology by which genomes of living organisms may be modified (Jeon, Teixeira et. al, 2021).

3. Conclusion

It is a demanding effort to dissect the functional specificity of these complex genes to refine their downstream targets. These attempts can also contribute towards the molecular characterization of stem cells using homeobox gene markers and their feasibility for tooth repair and regeneration. Future investigations should also involve the identifications of factors and signals controlling the gene modifying loci of transcriptional factors, which plays a critical role during embryonic development. Such developments not only will provide essential oral functions of missing or defective teeth, which is a kind of social handicap due to mastication, speech and aesthetic problems, but can improve the socio-cultural interactions of an individual resulting high impact on emotional well-being thereby representing a good life quality.

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Declaration of Conflict

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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