

## Development, Pathology and Regeneration of Dental and Orofacial Tissues: A Molecular Approach

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Neural crest cells contribute to the development of the teeth and orofacial primordia [1,2]. A large number of syndromes are known to be associated with orofacial disorders, such as defects in teeth, cleft lip and palate development [3]. Transgenic analyses in mice are carried out to determine the temporal and spatial requirement of involved genes in orofacial and tooth development. The identification of genes involved in dental pathology and regeneration contributes to our understanding on the regulatory mechanisms that control stem cell development [2]. The study of molecular mechanisms involved in human dental tissue regeneration, as well as in innovative treatments for reparative processes that require stem cell technology and growth factors delivery systems is of prime importance.

Teeth are the highest mineralized organs of the body. Human genetic studies have identified mutations in genes that affect dental structures such as enamel and dentin. Embryonic development of teeth relies on a series of reciprocal inductive signalling between between the oral epithelium and the cranial neural crest-derived mesenchyme. Separation and recombination of these two tissues in mice has shown that odontogenesis is induced by the epithelium and later the odontogenic potential switches to the mesenchyme [4]. This potential allows conditioning of the underlying mesenchyme, which in turn regulates the differentiation of epithelial cells. The importance of cranial neural crest cells in odontogenesis has been proven in experiments where transplantation of mouse neural crest cells into chick embryos allowed growth of tooth germs [5,6]. A variety of molecules have been shown to be involved in all stages of tooth development (i.e. initiation, morphogenesis, cytodifferentiation and mineralization processes). Members of the Transforming Growth Factor beta (TGF $\beta$ ) superfamily such as Bone Morphogenic Protein 2 (BMP2), BMP4 and BMP7 are important regulators of epithelial-mesenchymal interactions during odontogenesis [7]. Members of the Fibroblast Growth Factor (FGF) family such as FGF2, FGF3, FGF4, FGF8 and FGF10 are involved in dental cell proliferation and regulate expression of tooth specific genes [8]. Wnt proteins such as Wnt3, Wnt7b, Wnt10a and Wnt10b have been found to regulate cell proliferation, migration and differentiation during odontogenesis [8]. Other diffusible molecules such as sonic hedgehog (SHH) contribute to tooth initiation and morphogenesis [8]. Transcriptional regulators such as *Pitx1* and *Pitx2* are also very important for proper tooth development. *Pitx1* is expressed in tooth epithelium and its deletion affects molar tooth morphology (smaller molars with fewer cusps) [9]. Deletion of the *Pitx2* locus in mice results in loss of all dental structures. *Pitx2* is responsible for the Rieger syndrome in humans, an autosomal dominant disease characterized by dental hypoplasia and/or agenesis [8]. *Pitx1* and *Pitx2* expression is regulated by BMP and FGF signals [9]. All these studies highlight the importance of signaling molecules at early stages of tooth development. In spite of this wealth of information at the genetic and phenotypic level, only limited information exists on the molecular control that regulates the different steps of ameloblast differentiation and enamel formation and maturation [10]. The elucidation of these molecular mechanisms is crucial in order to design new therapeutic approaches to prevent and treat enamel defects in humans.

Over 300 genetic syndromes and a number of non-syndromic inherited conditions present enamel structural defects as phenotypic

traits. Amelogenesis Imperfecta (AI) is a term denoting generalized hereditary defects of enamel formation not associated with other major developmental defects [8] and occurs at an estimated incidence of 1:700 to 1:14.000 live births, depending on the populations studied. AI affects the structure and clinical appearance of enamel of all or nearly all the primary and permanent teeth in a more or less equal manner, and may also be associated with morphologic or biochemical changes elsewhere in the body. Extensive clinical analyses of patients with AI combined with genetic mapping experiments have been realized to elucidate how the AI phenotype is brought about. Despite the credible advances in genetics, the molecular and cellular mechanisms of the different steps leading to the generation of AI are not yet known.

Orofacial defects account for approximately one third of birth defects. The clinical management of orofacial defects is a major area of commitment requiring substantial resources. For example, growth problems associated with the mandible have a major clinical impact requiring surgical, dental, orthodontic, speech, hearing and psychological treatments. To understand how these defects arise, it is essential to understand how facial derivatives normally develop. The patterning of these derivatives is specified early in the embryo by genes that control cell fate within the embryonic orofacial primordia. The aetiology of orofacial defects is complex and thought to involve both major and minor genetic influences with variable interactions from environmental factors. Using a combination of gene targeting technology, molecular biology and traditional experimental embryology techniques, significant progress has been made in the identification of numerous genes and gene pathways critical for orofacial development. Important findings have recently come from studies involving syndromic forms of the disorders [11]. Human genetic studies have identified mutations in genes that affect facial patterning that in many cases have been experimentally shown to be important for orofacial development in mouse or other model organisms. A variety of signalling molecules have been implicated in facial primordia identity, development and differentiation. These include inductive signals such as SHH, WNT, FGFs, BMPs and other members of the TGF $\beta$  superfamily. Transcription factors such as the distal-less (Dlx) and Pitx families also play key roles in maxillary and mandibular specification and are regulated by BMP and FGF signals. Yet, an understanding of orofacial morphogenesis at the cellular and molecular level is prerequisite for developing a molecular rationale

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for the prevention and therapy of congenital and acquired orofacial anomalies.

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