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Review Article

Odontogenesis, Molecular Basis of Odontogenesis and its Relation with common Odontogenic Cysts and Odontogenic Tumors: A Review

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***ABSTRACT*:**
Embryonic development of teeth which is also called as Odontogenesis, relies on a series of reciprocal inductive signaling between two adjacent tissues, an epithelium and a mesenchyme. Regulatory genes are used sequentially throughout the development of the tooth organ, i.e. from tooth initiation to tooth patterning and histogenesis of the dental tissues which contribute to signalling pathways. Important signalling pathways that are involved in organogenesis include BMP, FGF, TNF, Shh, and Wnt pathways. In particular, the characteristics of odontogenic tumors and cysts appear to depend upon the molecular mechanisms associated with tooth development, bone metabolism and malignant potential of tumors. The detection of common signalling molecules in both healthy dental tissues and tumor samples suggest that the abberant activation of these genes might play a role in oncogenesis. This review presents the co-relationship between the molecular basis of genetic elements and relation between common odontogenic cysts and tumors.

Keywords Odontogenesis, odontogenic cysts, odontogenic tumors, regulatory genes.

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INTRODUCTION

Embryonic development of teeth which is also called as Odontogenesis, relies on a series of reciprocal inductive signaling between two adjacent tissues, an epithelium and a mesenchyme. The mesenchymal cells participating in tooth development form cranial neural crest (CNC) cells, which delaminate at the junction between the extreme dorsal surface of the neural tube and the ectoderm, and migrate extensively to populate the branchial arches.[1]

Enamel organ develops by proliferation of cells in dental lamina divided into 4 regions: the outer enamel epithelium, stellate reticulum, stratum intermedium and inner enamel epithelium. Cytodifferentiation of odontoblasts & ameloblasts, the cells forming dentin & enamel, starts at tip of future cusps.[2] Dental histomorphogenesis & cytodifferentiation are controlled by an alternative flux of information circulating between ecto-mesenchyme & epithelial cells. They are matrix mediated signals.[3]

Cysts and tumors derived from the odontogenic tissues constitute an unusually diverse group of lesions. This diversity reflects the complex development of the dental structures, since these lesions all originate through some alteration from the normal pattern of odontogenesis. Some lesions included in this category may in fact not represent neoplasia at all, but are only minor alterations in the normal process of tooth development.[4]

MOLECUALR BASIS OF ODONTOGENESIS

Regulatory genes are used sequentially throughout the development of the tooth organ, i.e. from tooth initiation to tooth patterning and histogenesis of the dental tissues.[2] Important signalling pathways that are involved in organogenesis include BMP, FGF, TNF, Shh, and Wnt pathways. Most of these cascades are essential for many aspects of embryogenesis and their signalling molecules have been shown to have diverse biological functions, such as cell fate determination, cell proliferation and differentiation, and histodifferentiation.[1]

The oral epithelium initiates tooth development by signaling through generic molecules including FGFs, BMPs, Wnt and SHH to the underlying neural crest derived mesenchyme at 9–11 embryonic days. These early molecular events are accompanied by localized thickenings of the oral epithelium at the position of the future teeth. Re-use of the BMP and FGF signaling cascades together with other signals such as activin A is implicated in the regulation of tooth bud formation, which is accompanied by mesenchymal cell condensation around the tooth germs. [1]

Pax-9 expression in defined areas of mesenchyme determines the site of tooth initiation. Shh is related to timing of bud formation. Signals from mesenchyme precede epithelial signals which are responsible for regionalizing oral epithelium.[3] Msx-1 is predominantly expressed in mesenchymal cells during tooth development, whereas Msx-2 is expressed in both mesenchymal and epithelial cells. Msx-2 expression at the epithelial stage of development immediately prior to bud formation was found to be transient and localized to the thickened epithelium (placode), which becomes incorporated into the tooth bud as it undergoes invagination.[3]

Expression of these genes in ectomesenchymal tissues may control the development & ultimate shape of tooth. Homeobox genes (Dlx, Pax, Msx etc) are widely expressed in embryonic craniofacial tissues. The odontogenic pattern is determined by early regional & restricted expression of various combinations of homeobox genes. [3]

Epithelial cells make BMP-4 until cap stage, when production of BMP-4 shifts to condensed ectomesenchymal cells. Later BMP-2 is expressed in epithelial cells. BMP-4 activates Msx genes in adjacent ectomesenchymal cells. They are implicated as regulators of mesiodistal axis of tooth bud placement & they also regulate expressions of BMPs, syndecans in condensing ectomesenchyme. Transcription products of Msx-1 functions to regulate differentiation of ameloblasts & odontoblasts.[3]

Role of Enamel knot

The enamel knot is a transient population of cells in the center of the invaginating dental epithelium in close contact with the underlying dental mesenchyme. Shh, BMP 2, and BMP 7 are all expressed in the enamel knot at E13, p21 acts by inhibiting the ability of G_1 cyclins to phosphorylate the retinoblastoma protein (Rb). The Rb protein thus remains active and acts as a tumor suppresser gene by promoting exit from the G_1 phase of the cell cycle. The enamel knot expresses FGF-4, BMP-4 and BMP-7. FGF-4 has been shown to prevent apoptosis in dental mesenchyme. The timing of apoptosis may influence the morphology of the tooth cusps.

Cellular retinoic acid binding proteins transmit signals of retinoic acid. They are expressed in developing tooth wherever high rates of cell proliferation is present. One of these proteins CRABP-1 appears to be expressed by secretory but not maturation stage of ameloblasts. Members of TGF- β family are involved in the withdrawal of the cells that will become odontoblasts from mitotic cycle.[5]

BMP, SHH & FGF are important during later stages of tooth development. Both BMP 2 & BMP 7 are expressed in IEE across from differentiating odontoblasts. When cap stage starts, the level of EGF binding decreases in epithelial cells but increases in ectomesenchymal cells. Another regulated protein is midkine (MK). The differential or appositional localization of MK mRNA & MK protein in developing dental ectomesenchyme & its receptors on IEE cells provides a situation of epithelial-ectomesenchymal interaction.[6]

In root development, on a molecular level the most striking difference is the absence of some of the key genes involved in the regulation of the epithelial stem cell compartment. Patches of Notch1 and 3 were associated with blood vessels in the dental mesenchyme. Strong expression also found in Hertwig's epithelial root sheath, the outer enamel epithelium and the epithelium covering the crown and absent in the ameloblasts. Lfng also expresses in Hertwig's root sheath and remainder of the tooth, except for some light expression in the mesenchyme near the root tips, likely representing the differentiating odontoblasts.[7]

ASSOCIATION WITH COMMON ODONTOGENIC CYSTS

According to International Medical College (2002), cyst is defined as a unilocular or multilocular, epithelium lined cavity of various aetiologies that contain liquid or gaseous materials. The cystic changes involving the odontogenic apparatus give rise to a group of lesions called as odontogenic cysts. Odontogenic cysts account for 7–13% of the lesions diagnosed in the oral cavity.[8]

Odontogenic Keratocyst (OKC)- Various cytokines like TGF-β,TNF,OAF & prostaglandins are known to cause bone resorption. PGE_2, PGE_3 & IL-1 are the prime

molecules for osteolysis. Odontogenic Keratocyst however, have a high PG level but the amount of bone resorption is less than radicular cysts as thin walled OKC secrete less bone resorbing factors/unit surface area than radicular cyst.[9]

All OKC cysts released IL-1 and IL-6 bioactivity. It was observed that positive pressure may have a crucial role in OKC growth by stimulating the expression of IL-1α in the epithelial cells.[10] MMP-2 and MMP-8 were also present, but to a lesser extent. Mast cell tryptase (MCT) was also detected. [11]The epithelial cells isolated from the OKCs secreted IL-1α and proMMP-9 without stimulation. IL-1α may up-regulate not only proMMP-9 secretion but also proMMP-9 activation by inducing proMMP-3 and uPA production in the epithelial cells by autocrine/paracrine regulatory mechanisms fluids.[12]

Dentigerous cyst- Data reported by Harris (1978) indicated a lower level of prostaglandin-like material (measured as PGE2) released by dentigerous cysts (12.2±9.4 ng/mg) than by radicular (16.6±13ng/mg) or by OKCs (20±11ng/mg).[13] LOH observed in the epithelial lining of the dentigerous cysts suggested that a decisive initiating event in their development, as in the development of the OKCs, is PTCH inactivation in a progenitor epithelial cell from which the entire epithelial lining is later cloned. They also found that PTCH mRNA detected in these dentigerous cysts showed that the gene was expressed despite alterations or deletions that were detected as LOH, so at least the other allele was being transcribed. They concluded that since the expression indicated SHH continued signalling, that allele must also have mutated; otherwise, its product would have blocked the pathway signalling.[14]

Calcifying Odontogenic cyst (COC)- In COC, Bax, an apoptotic protein is expressed in ghost cells. In contrast, the nucleated cells adjacent to ghost cells exhibited both Bax and BaXL. This suggests, ghost cells are formed during terminal differentiation as an apoptotic process. COC is caused by an activating mutation of β-catenin.[15]

Radicular Cyst- Periapical lesions, as well as periodontal disease, seems to have cyclic patterns of evolution. Periods of burst may be intercalated with periods of quiescence. Because keratinocyte division must occur during cyst growth, it is presumed that epithelium status could indicate the biological activity of radicular cysts. Increased proportions of Th2 cells in cysts with hyperplastic epithelium. Th2 cells could be associated with radicular cyst growth. [16]

Apoptosis was always present in the epithelium of the cyst and was more frequent in lesions with atrophic (quiescent) epithelium. Higher levels of bcl-2 seen in atrophic epithelium. [17] A greater percentage of CD57+ cells in RC with atrophic epithelium compared to hyperplastic epithelium. CD57 antigen is an important modulator of the immune system and is indicative of immunosuppression, it may constitute a negative immunomodulator of RC's epithelium growth.[18]

ASSOCIATION WITH COMMON ODONTOGENIC TUMORS

Odontogenic tumors are derived from these tissues or from their derivatives, exhibiting considerable histologic variation, and are classified into several benign and malignant entities. Recent studies have identified genetic and molecular alterations in epithelial odontogenic tumors however, details of the mechanism of oncogenesis, cytodifferentiation, and tumor progression remain unknown.[19]

Epithelial–mesenchymal transition (EMT) is a complete switch of epithelial cell properties characterized by phenotypic conversion in which epithelial cells lose their polarity and cohesiveness and acquire migratory features and the characteristics of fibroblasts. Such gain of migratory capability and autonomous cell survival underlies the development of invasive and metastatic tumors.[20]

Ameloblastoma- Epithelial odontogenic tumors retained their expression of E-cadherin in the central areas of tumor nests, although there was decreased expression in areas of cell–cell contact at the periphery. MMPs can be secreted by neighbouring cells and can become localized and activated on the surface of migrating endothelial cells. According to a study to evaluate the roles of extracellular matrix (ECM)-degrading serine proteinase in progression of odontogenic tumors, expression of urokinase-type plasminogen activator (uPA), uPA receptor (uPAR), plasminogen activator inhibitor-1 (PAI-1), and maspin in ameloblastic tumors and was analysed in tooth germs as well.

Differences in p53 protein expression in different types of ameloblastomas have implicated tumor suppressor gene alteration as a potential oncogenic mechanism. Apoptotic cell death in ameloblastomas is increased, suggesting that the apoptosis pathways may be also involved in tumorigenesis.[21] The FOS gene-oncogene and tumour-necrosis-factor-receptor-1 were the most overexpressed genes. Ten genes, including sonic hedgehog (SHH), cadherins 12 and 13 and transforming growth-factor-ß, is under-expressed in all ameloblastomas studied.[22]

Adenomatoid Odontogenic Tumor (AOT)- In the AOT, PCNA revealed that the cells in the spindled areas and in the peripheral cords were the most proliferative, which could suggest that those sites would be responsible for the tumoral growth. HGF expression was detected in tumor cells, and was especially prominent in pseudoglandular cells in duct-like structures. A strong reaction to BMP-2, BMP-4, BMP-7, BMPRs and CBFA1 was found in tumor spindle cells in whorled nodules and pseudoglandular cells in duct-like microcysts.[23]

Calcifying epithelial Odontogenic Tumor (CEOT)- It was demonstrated the presence of AMBN gene mutations in adenomatoid odontogenic tumor suggesting that both AOT and CEOT share at least some common genetic pathways-Wnt, BMP,SHH etc. Additional genetic or

epigenetic damage in CEOT could explain its distinct local invasiveness growth. High molecular weight (mw) CKs, CK-1, CK-5 and CK-14 were detected by Kumamoto et al; the finding of CK-14 were confirmed by others.[24]

Squamous Odontogenic Tumor (SOT)- Notch1, 3 and 4, Jagged1 and Delta1 were expressed by the peripheral and central cells of the tumor islands in the SOT as well as in areas of keratinization, cystic degeneration, clear cell differentiation and dystrophic calcification foci. Mutations of the Ameloblastin gene, which in human maps to chromosome 4q21 have been detected in SOT as well as ameloblastoma and AOT and were considered tumor specific mutations. [25]

DISCUSSION

The common behavioural feature of all cysts is the stimulation of residual developmental epithelial cells leading to proliferation but not invasion of adjacent tissues. As the mass enlarges, the epithelial cells in the centre become positioned further away from the blood supply at the periphery of the mass. At some point, usually 180-200µm, the cells at the centre become too far removed from the nearest blood vessel to survive by nutritional diffusion. They die, creating a lumen. Their intracellular products make the lumen hypertonic, which transudates fluid into the lumen. This will create a hydrostatic pressure, producing bone resorption, clinical expansion and sometimes mild paraesthesia or pain. As additional epithelial cells die off and are sloughed into the lumen, their contents perpetuate the hypertonic state and the hydrostatic pressure.. As the cyst enlarges, it compresses surrounding connective tissue into a connective tissue wall. The epithelial lining matures and develops a basement membrane. The cyst lining continues to proliferate, thus causing the cyst to enlarge until it is removed/enucleated. The proliferating cells are communicated into the oral cavity, external surface so as to break the proliferation hydrostatic pressure cycle and the inciting cytokine stimulus is removed.[26]

Odontogenic tumors from ectodermal origin, as ameloblastomas, are recognized to arise from remnants of the odontogenic epithelium. However, the specific causative mechanisms remain unknown. In particular, the characteristics of odontogenic tumors and cysts appear to depend upon the molecular mechanisms associated with tooth development, bone metabolism and malignant potential of tumors. The detection of common signaling molecules in both healthy dental tissues and tumor samples suggest that the abberant activation of these genes might play a role in oncogenesis. Studies concerning this area are recent and an attempt to unravel these hypotheses.[27]

CONCLUSION

Further investigations on the regulation of genes involved in the pathological development of odontogenic lesions, as well as the coordination amongst them may provide a better understanding of the process, leading to the development of more efficient diagnosis, prevention and treatment approaches.

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