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Standard Review

Genetic aspects of ameloblastoma: a brief review

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Ameloblastomas are defined as aggressive neoplasms arising from the odontogenic epithelium which exhibit a locally invasive behavior with a high rate of recurrence. If left untreated, they often lead to extensive tissue destruction and deformity. Due to the fact that these tumors emerge from remnants of normal odontogenic apparatus, which is strictly regulated through several genes, studies have been done in an attempt to unravel the relation between these two processes. The normal genetic regulation takes place through different signaling pathways, including four major families: TGFβ [Transforming Growth Factors, which include BMPs (Bone Morphogenetic Proteins)], FGF (Fibroblast Growth Factors), Hh (Hedgehogs) and Wnt (Wingless). Each family consists of several signals encoded by different genes. The unraveling of specific details concerning these genes and the mechanisms whereby the expression and relationships among them are mediated, may provide an opportunity to develop new treatment therapies and afford efficient prevention.

Key words: Ameloblastoma, sonic hedgehog, bone morphogenetic protein, fibroblast growth factor, wingless.

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INTRODUCTION

The first morphological sign of tooth development is a thickening and a down growth of the oral epithelium, which subsequently buds into the underlying mesenchyme (Thesleff and Sharpe, 1997). In fact, the basal cell layer of the oral epithelium forms a solid tube-like structure termed the dental lamina, which infiltrates the connective tissue. This process is termed invagination. The budding of the lamina also marks the shifting of inductive potential from the tooth epithelium to the mesenchyme (Jernvall and Thesleff, 2000). The subsequent formation of a defined epithelial bud into the mesenchymal tissue marks the first stage of tooth development, the so-called bud stage (Figure 1A) (Eversole al et al., 2004). Progressively, the round epithelial bud gains a concave forma, and now enters the cap stage of development (Figure 1B) (Eversole et al., 2004; Avery, 1992). In this stage three different structures can be recognized: the enamel organ, the dental papilla, which gives rise to the tooth pulp and the odontoblasts, and the cells surrounding these structures known as the dental follicle (Thesleff and Sharpe, 1997; Avery, 1992). The latter remains around the tooth until it erupts. As this happens, the crown portion of the dental follicle becomes part of the connective tissue of the free marginal gingival and its root portion initiates formation of the periodontal ligament (Eversole et al., 2004). Additionally, the enamel organ is responsible for deter-mining the shape of the crown, initiating dentin formation, establishing the dento-gingival junction and the enamel formation of the deve-

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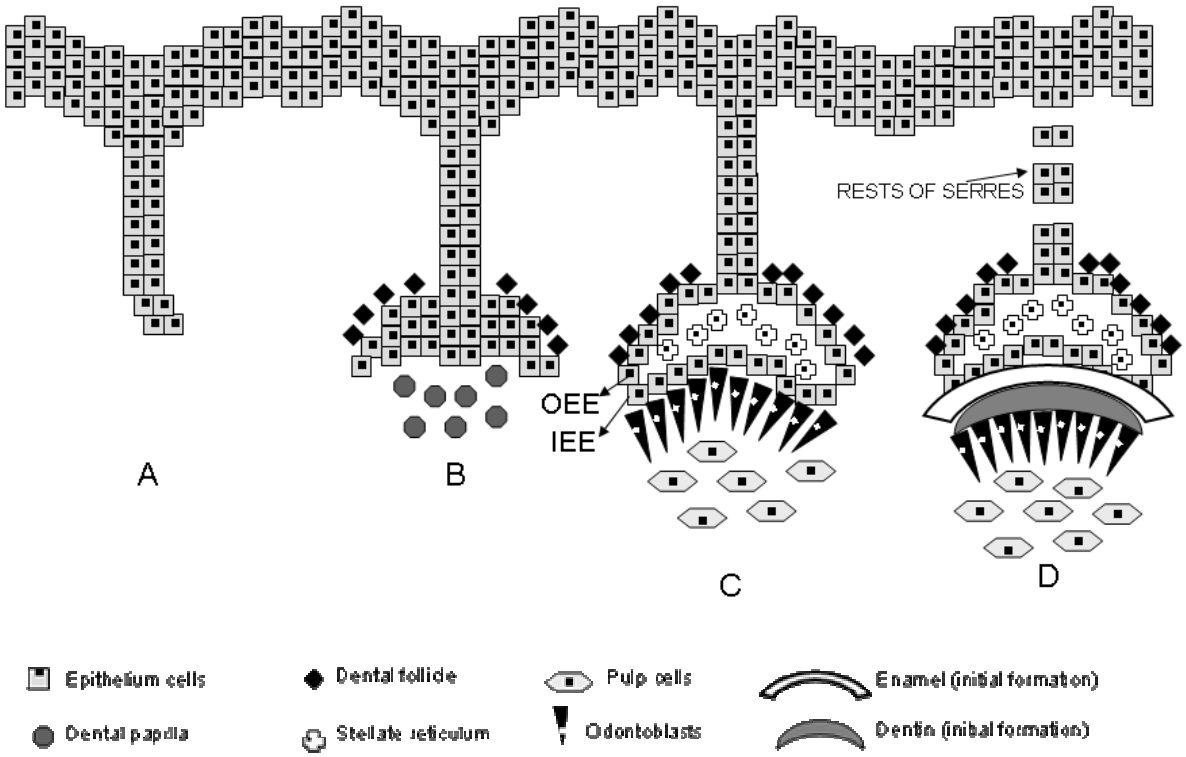

Figure 1. Schematic representation of the early stages of tooth development. A = Invagination / Bud stage; B = Cap stage; C = Early bell stage; D = Late bell stage. OEE = Outer Enamel Epithelium; IEE = Inner enamel epithelium. (Adapted from Eversole LR, Wysocki GW, Sapp P 2003).

developing tooth germ (Tsujigiwa et al., 2005).

As odontogenesis advances, the cap-shaped structure enlarges and the bottom layer of the epithelium (inner enamel epithelium) separates from the top layer (outer enamel epithelium). The inner layer will determine the shape of the future tooth crown specific for that location, while the outer layer becomes associated with a capillary plexus whose function is to bring nutrition to the cells of the enamel organ (Eversole et al., 2004; Avery, 1992). The intermediate zone between inner and outer enamel epithelium is composed of loosely arranged star-shaped epithelial cells termed the stellate reticulum. This stage is defined as the early bell stage (Figure 1C) (Eversole et al., 2004), and an initial differentiation is apparent. The cells from the inner enamel epithelium elongate and differentiate into pre-secretory ameloblasts which turn into the future enamel-forming cells. Adjacent to this layer, spindle-shaped cells, referred to as stratum intermedium, appear and function with the ameloblasts in the formation of enamel. The same initial differentiation occurs within the peripheral cells of the dental papilla, and they are now called pre-secretory odontoblasts and will function in dentin formation (Avery 1992). This event takes place at the interface of the epithelium and mesenchyme and is regulated by interactions between the two tissues (Thesleff and Sharpe, 1997; Ruch et al., 1995; Thesleff and Åberg, 1997).

During the late bell stage (Figure 1D) occurs the beginning of the deposition of matrix. As ameloblasts mature, they stimulate the odontoblasts to secrete a collagenous extracellular matrix which subsequently mineralizes into dentin, a bone-like hard tissue (Thesleff and Sharpe, 1997; Miletich and Sharpe, 2004). After a few micrometers of dentin deposition, the ameloblasts secrete a non-collagenous enamel matrix, composed primarily of amelogenins, which subsequently mineralizes (Avery, 1992; Ten Cate, 1994). Another important feature of this stage is the initial degeneration of the dental lamina, and, consequently, the enamel organ becomes separated from the oral epithelium. The islands of epithelium that are formed from the remnants of dental lamina in the connective tissue are termed rests of dental lamina or rests of Serres (Miyake et al., 2006). In the end of the developmental process, the epithelial cells undergo lysis and the dental lamina disappears (Avery, 1992).

After crown morphogenesis, the roots of the teeth develop and subsequently the teeth erupt into the oral cavity (Thesleff and Sharpe, 1997; Ten Cate, 1994).

Thus, the entire mechanism of tooth development occurs through interactions between epithelium and mesenchyme. This communication is strictly coordinated by several genes and takes place through different signaling pathways. Four major families of genes are involved in this process: TGFβ (Transforming Growth

Table 1. Gene expression in epithelium and mesenchyme during tooth development. Note that the gene Sonic Hedgehog is present in the epithelium from the bud to the bell stage, but it is absent in the mesenchyme during the entire process. However, it is related to epithelial-mesenchymal interactions.

Gene	Epithelium	Mesenchyme
SHH	Positive	Negative
BMP	-2, -4, -7	-3, -4, -6
FGF	-1, -4, -8, -9, -20	-1, -2, -3, -7, -10
WNT	-3, -4, -5a, -6, -7b, -10a, -10b	-5a

SHH: Sonic Hedgehog; BMP: Bone Morphogenetic Protein; FGF: Fibroblast Growth Factor; WNT: Wingless. For related authors and references, please refer to text.

Factors, which include BMPs (Bone Morphogenetic Protein) FGF, (Fibroblast Growth Factors), Hh (Hedgehogs), and Wnt (Wingless). Each of them has specific functions, as described in the following sections of this review. A summary of the expression of these genes during normal tooth development can be seen in Table 1.

Ameloblastomas

Odontogenic tumors are lesions originating from epithelial and/or mesenchymal components of the tooth-forming apparatus (Kumamoto, 2006; Reichart and Philipsen, 2004; Takata et al., 2000). They are unique to the jaws and if left untreated, often lead to extensive tissue destruction and deformity (Miyake, 2006). They comprise a complex group of lesions that exhibit diverse histological patterns and various clinical behaviors (Takata et al., 2000; Kramer et al., 1992). These developmental-associated tumors are generally benign, although several reveal a neoplastic nature and show locally invasive behavior with a high risk of recurrence. Due to their histological similarities to the developing tooth tissues in normal odontogenesis, the correlation among them is the basis for their classification. Hence, tissues resembling odontogenic epithelium, enamel organ, dental enamel, dentin and cementum are often observed in various types of odontogenic lesions (Takata et al., 2000).

Ameloblastoma is the most frequent odontogenic tumor arising from dental epithelium, and is characterized by its histological resemblance to the enamel organ of the developing tooth germ (Kramer et al., 1992; Perdigao et al., 2004; Melrose, 1999; Nagatsuka et al., 2005), yet enamel formation is not observed (Tsujigiwa et al., 2005). These lesions are rare in children and the greatest period of prevalence occurs in the age range of 20 to 50 years (Nagatsuka et al., 2005; Greenberg and Glick, 2003). However, as they are characterized by slow-growth, their develop-ment probably initiate in childhood (Huang et al., 2007). The main area of incidence is the mandible, and over two-thirds occur in the molar-ramus region (Greenberg and Glick, 2003). Microscopically, all ameloblastomas show a fibrous stroma, with islands or strands of proliferating epithelium cells arranged in a palisade manner (Nagatsika et al., 2005; Greenberg and Glick, 2003). There is considerable variation in histological patterns, and classification within this context comprises follicular, plexiform, acanthomatous, granular cell, basal cell and desmoplastic types. Of these, the follicular and plexiform types are the most common (Kumamoto et al., 2005). These histologic variants show no correspond-dence with either the clinical appearance of the tumor or its behavior, and different sections of the same lesion may show one or the other histologic type (Greenberg and Glick, 2003).

Although defined as a benign neoplasm, ameloblastomas are locally destructive and a high rate of recurrence is observed if the lesions are not entirely excised (Miyake et al., 2006; Huang et al., 2007; Eversole et al., 2004). A few cases of tumor-to-tumor metastasis as well as malignant transformation with distant metastasis have been reported in the literature (Huang et al., 2007; Sahoo et al., 2007). The cause of their local invasiveness remains unknown. Several studies have been done in an attempt to clarify this phenomenon. Therefore, it is believed that this process involves the rupture of the basement membrane and the surrounding extracellular matrix with subsequent growth and proliferation of tumor cells. The invasive ability of ameloblastoma is also thought to be related to the release of biologically active molecules produced, such as matrix metalloproteinases, which in turn trigger mitogens to be released randomly, contributing to the cellular proliferation of ameloblastoma cells (Nagatsuka et al., 2005; Pinheiro et al., 2004).

Genetic and cytogenetic alterations in their structure were detected by several recent investigations. However, further studies are needed to unravel the mechanisms of oncogenesis, cytodifferentiation, and tumor progression (Miyake et al., 2006; Kumamoto et al., 2005; Heikinheimo et al., 2002).

The purpose of this article is to review the current knowledge regarding the gene expression and regulation in ameloblastomas, involving developmentally related genes such as: Sonic Hedgehog (SHH), Bone Morphogenetic Protein (BMP), Fibroblasts Growth Factor (FGF), and Wingless (WNT) and their co-expressed partners.

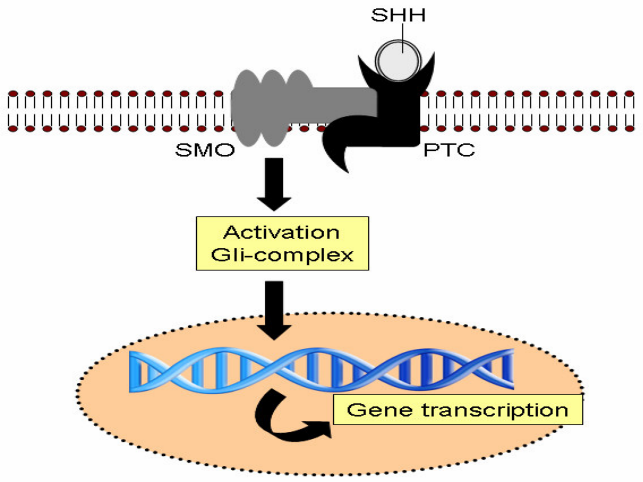

Figure 2. Simplified sonic hedgehog (SHH) signaling pathway. SMO = Smoothened (receptor); PTC = Patched (receptor); Gli family (transcription factors).(Adapted from Gilbert, 2000).

Sonic hedgehogs

Sonic Hedgehogs (SHH) are members of the Hedgehog family and have been recognized to act in many fundamental processes in normal embryonic development, such as growth, patterning and morphogenesis (Cobourne et al., 2004; Ingham and McMahon, 2001). The signal is received within a target tissue by the receptor patched (PTC), which is believed to combine with Smoothened (SMO), a second, multi-pass membrane protein that leads to the transduction of the signal. In the resting state, PTC normally represses SMO. The release of this inhibition occurs when the SHH signal binds to PTC, allowing SMO to activate the Gli-family zinc-finger transcription factors (Figure 2) (Zhang et al., 2006; Gritli-Linde et al., 2002; McMahon, 2000).

During the normal process of tooth development, the expression of these molecules from the bud to the bell stage supports the proposal that they might regulate the growth and determine the shape of the tooth (Jernvall and Thesleff, 2000; Cobourne et al., 2004; Zhang et al., 2006). Control of cell-cell interactions and cell prolixferation in tissue patterning during development has been reported to be associated with this pathway. Detection of SHH in human tooth germ tissues in various developmental stages show that they are related to epithelial-mesenchymal interactions during tooth development (Kumamoto et al., 2004).

Alterations in SHH-pathway genes have been linked to a variety of developmental defects, and there is evidence of tumor formation resulting from aberrant activation of this pathway in adult life (Kumamoto et al., 2004). Other studies also indicate that there may be a relation between the developmental process and oncogenesis (Heikinheimo et al., 2002).

Investigations regarding the expression of SHH in ameloblastomas have been done in order to unravel its potential involvement. A study in 2002 (Heikinheimo et al., 2002) utilized cDNA microarray technique to investtigate the gene expression patterns in three types of ameloblastomas: follicular, plexiform and acanthomatous. Although several other genes have shown high levels of expression when compared to the control, genes for SHH were found to be repressed in all samples. These results were confirmed by real-time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) (Heikinheimo et al. 2002).

Immunohistochemical investigations have shown a lower expression of SHH in stromal cells of the tumor compared with mesenchymal cells in tooth germs (Kumamoto et al. 2004). However, strong detection in the cytoplasm of cellular components of the neoplastic tissues, mainly in peripheral columnar or cuboid cells was encountered (Zhang et al., 2006; Kumamoto et al., 2004). Considering that follicular and plexiform ameloblastomas showed a predominant expression of SHH signaling pathway protein in the epithelial components and taking into account the functions of SHH in normal dental tissues, there is evidence that these molecules might regulate the proliferation of tumor epithelial cells. An autocrine mechanism of activation is also suggested (Zhang et al., 2006).

Nevertheless, further studies are necessary to clearly indicate the specific role of SHH signal transduction in the oncogenesis of odontogenic epithelium.

Bone morphogenetic proteins

Bone Morphogenetic Protein (BMP), a component of the transforming growth factor (TGF) superfamily, is defined as a mesenchymal cell differentiation factor and is classified as a morphogen (Moghadam et al., 2001). It is thought to play a critical role in cell proliferation, differrentiation, chemotaxis, extracellular matrix production and apoptosis during developmental processes (Yamaguchi et al., 2000; Kumamoto and Ooya, 2006; Tompkins, 2006). Investigations have suggested that these proteins are not only involved in the mechanism of bone formation, but also in the differentiation of neoplastic tissues (Yang and Jin, 1990; Gao et al., 1997).

Two types of receptors have been thought to act in this signaling cascade, the BMP receptors (BMPR) type I and type II (BMPRI and BMPRII). The Type I receptor bind the BMP proteins with higher affinity, and the conesquence of this binding is the activation of Smad proteins through phosphorylation, triggering the intracellular signaling pathway (Figure 3) (Nohe et al., 2004; Nie et al., 2006). It has been suggested that BMPs are involved in the activation of other kinase cascades such as MAPK, PI3 kinase, and PKC (Kishigami and Mishina, 2005). Members of the BMP family have been identified to play an important role in the normal process of tooth development, especially concerning epithelial-mesenchymal interactions. BMP-2, BMP-4 and BMP-7 are express-

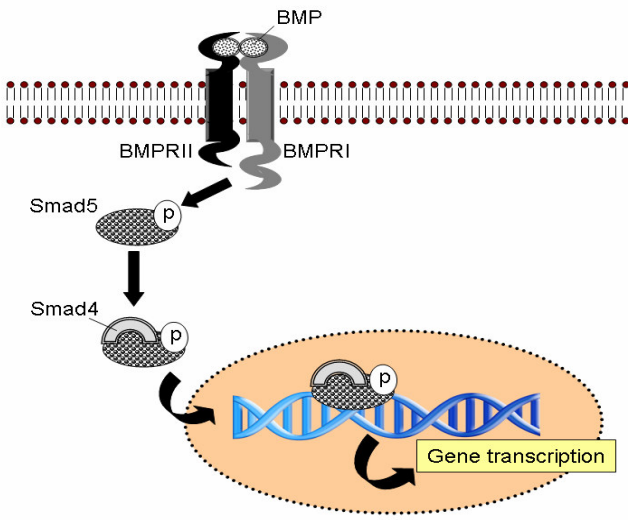

Figure 3. Schematic representation of Bone Morphogenetic Protein (BMP) signaling pathway. After the binding of the BMP protein to the receptors, Smad5 proteins are phosphorylated and trigger the entire intracellular cascade. BMPRI = BMP Receptor type I; BMPRII = BMP Receptor type II, (Adapted from Gilbert, 2000).

ed in dental epithelia in the initial stages of tooth formation (Tompkins, 2006; Nie et al., 2006) and are thought to act as a signaling center in the developing teeth (Vaahtokari et al., 1996; Iseki et al., 1995). The expression of these BMPs was found to shift between epithelium and mesenchyme during the subsequent steps of morphogenesis, suggesting a potential role in the mechanisms of induction, as well as an association with the expression of other genes, such as MSX1 and MSX2 and SHH (Thesleff and Sharpe, 1997; Maas and Bei, 1997; Zhang et al., 2000). The cascade involving MSX1 and MSX2 are related with epithelial-mesenchymal interactions during the stages of tooth initiation and crown morphogenesis (Nie et al., 2006). In addition, it was demonstrated that the SHH signal is maintained and regulated by BMP-4 in a concentration-dependant manner (Zhang et al., 2000).

Furthermore, recognition of BMPs in several neoplasms, such as malignant fibrous histiocytoma, liposarcoma, leiomyosarcoma, salivary gland tumors, prostate hyperplasia, adenocarcinoma, and ovarian tumors, as well as osteosarcoma and chondrosarcoma suggest that they may be associated with both pathological mineralization and tumor development and progression (Kumamoto and Ooya, 2006; Gao et al., 1997; Jin et al., 2001). Within this perspective, recent investigations concerning odontogenic tumors have been made in an attempt to confirm this hypothesis.

A mouse monoclonal antibody against bovine BMP (BMPMcAb) was utilized in an immunohistochemical study of 20 cases of ameloblastoma (Gao et al., 1997). Although ameloblasts of control tooth germs were positively stained, none of the tumor samples showed expression for BMPMcAb. The authors advocate that immature tumor cells cannot synthesize detectable levels of BMP, and the degree of differentiation of the odontogenic epithelium present in ameloblastomas might influence the identification of such proteins (Gao et al., 1997).

Conversely, another investigation (Kumamoto and Ooya, 2006) revealed expression of BMP-2, -4 and -7, BMPRI and BMPRII in ameloblastoma samples through RT-PCR (Reverse-Trancriptase Chain Reaction) and Immunohistochemistry. Messenger RNA transcripts for BMPs and their receptors were identified in all types of ameloblastoma tested. Immunostaining for these molecules was evident in neoplastic cells neighboring the basement membrane of the tumors, suggesting that they might influence the cytodifferentiation of neoplastic odontogenic epithelium. Additionally, strong reactivity for BMP-7 found in keratinizing cells of acanthomatous ameloblastoma advocates an association with cell death of neoplastic odontogenic epithelium (Kumamoto and Ooya 2006).

Fibroblast growth factors

FGF signaling plays strategic roles in embryonic development and differentiation. Expression of FGF-3, -4, -7, -8, -9, -10, and -20 have been identified in the tooth (Tompkins, 2006). In effect, epithelial expression comprises the factors FGF-4, -8, -9, and -20, whereas FGF-3, -7, and -10 are mostly found in the mesenchyme (Tompkins, 2006; Kettunen and Thesleff, 1998). The wide expression of FGF-9 in the dental epithelium of the bell stage suggests that this molecule is associated with the terminal differentiation of odontoblasts and ameloblasts (Kettunen and Thesleff, 1998).

Additionally, it has been proposed that FGFs regulate pattern and growth, as they are potent stimulators of cell proliferation. They also stimulate cell division in both dental mesenchyme and epithelium at several stages of tooth morphogenesis (Thesleff and Sharpe, 1997; So et al., 2001). FGF-1 has been described as a mitogenic and angiogenic factor in several tissues, including endothelial, neuronal, kidney, prostate, cardiac muscle, and smooth muscle cells. Although nuclear localization has been detected, it is usually encountered in the cytoplasm (Galzie et al., 1997). FGF-2 is found in a broader range of tissues than FGF-1 (Galzie et al., 1997). Like FGF-1, it is thought to be retained in the cytoplasm, even though nuclear localization was distinguished in embryonic development (Klein et al., 1997).

Little is known regarding the function of FGFs in pathological tissues, although there is evidence that they might be involved in neoplastic processes. Immunohistochemical localization of FGF-1 and -2 in ameloblastomas showed a similar staining to that found in normal dental follicles. The latter demonstrated a more

intense reactivity than the former, mainly in the cytoplasm of all layers of odontogenic epithelium. FGF-1 exhibited only weak focal staining, mostly in areas exhibiting squamous differentiation with little staining of the peripheral cells. The generalized lack of FGF-1 both in human ameloblastoma and normal dental follicles suggests that this growth factor is not significant in the process of odontogenesis, cyst formation, neoplastic transformation or tumor growth (So et al., 2001).

Concerning the presence of FGF-2 in both normal dental follicle and odontogenic tumor epithelium, the authors suggest that these growth factors may conduct the process of odontogenic differentiation rather than a pathological alteration in tumor formation. However, another possibility is that the cells of normal dental follicles may be incorporated into the odontogenic tumor epithelium; thus the expression of FGF-2 was similar (So et al., 2001).

Immunolocalization of FGF-1 and FGF-2 in cultured ameloblastoma epithelial cells revealed intense reactivity in the cytoplasm. Additionally, a growth enhancement of 2.5-fold was encountered when those molecules were added in serum-free culture. Immunoreactivity in ameloblastoma tissues was found for both FGF-1 and FGF-2, although a clear difference in their localization was distinguished in the sections. Ameloblast-like cells and stellate reticulum-like cells presented a high expression of FGF-1, whereas FGF-2 was identified mainly in the basement membrane. These results imply distinct roles for both molecules. FGF-1 might be associated with an autocrine mechanism of tumor growth, while FGF-2 would be involved not only in growth, but in the invasion process through the induction of proteases (Myoken et al., 1995).

Therefore, further studies are needed to confirm the specific roles of both FGF-1 and FGF-2 in neoplastic tissues, as controversies regarding this matter are still apparent in the literature.

Wingless

The WNT signaling pathway has been shown to regulate several developmental processes, including embryonic axis formation and organogenesis of the nervous system, heart, kidney, mammary gland, hair follicles and teeth (Kumamoto and Ooya, 2005; Sarkar and Sharpe, 1999).

This is accomplished by control of cell proliferation, morphology and motility (Kumamoto and Ooya, 2005). Several WNT genes are expressed during tooth development. WNT-3, -4, -6, -7b, -10a, and -10b are encountered in the epithelium only, whereas WNT -5a is expressed in both the epithelium and mesenchyme (Tompkins, 2006). They are regulated by the levels of an intracellular protein, β-catenin, and there is evidence that they may be involved in the formation of the tooth bud and in the process of amelogenesis (Thesleff and Sharpe, 1997; Kumamoto and Ooya, 2005).

Although mutations in β-catenin gene have been reported in several human tumors, these abnormalities are not common in ameloblastomas (Miyake et al., 2006). Usually, mutations in that gene lead to its accumulation in the nucleus, where it might elicit the activation of other factors implicated in tumor formation (Kumamoto and Ooya, 2005; Polakis, 2000). Studies of this nature found no significant relation between these alterations and the development of ameloblastomas, albeit there is evidence that the deregulation of the WNT signaling pathway might be associated with this pathological process (Miyake et al., 2006; Sekine et al., 2003).

β-catenin reactivity was examined in epithelial odontogenic tumors. The membrane and cytoplasm of most neoplastic cells of ameloblastomas were found to contain this molecule. These characteristics advocate that β-catenin may be associated with cell-cell adhesion and signal transduction in neoplastic odontogenic epithelium. Nuclear β-catenin expression was detected in some ameloblastomas as well, although it was not identified in tooth germs (Kumamoto and Ooya, 2005).

Thus, despite the evidence that the deregulation of the WNT signaling pathway might influence the development of ameloblastomas, further studies are needed to clarify its function in oncogenesis and tumor cytodifferentiation.

Conclusions

The normal process of tooth development is a sequence of events tightly coordinated by several signaling molecules. Interactions between tissues from different origins – ectodermal and mesodermal –, are regulated by these molecules, and as a result, the developmental event takes place.

Odontogenic tumors from ectodermal origin, as ameloblastomas, are recognized to arise from remnants of the odontogenic epithelium. However, the specific causative mechanisms remain unknown. 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. Further investigations on the regulation of genes involved in the pathological develop-ment of ameloblastomas, 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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