J Oral Pathol Med (2006) 35: 65–74

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REVIEW ARTICLE

Molecular pathology of odontogenic tumors

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Odontogenic tumors are lesions derived from the elements of the tooth-forming apparatus and are found exclusively within the jawbones. This review represents a contemporary outline of our current understanding of the molecular and genetic alterations associated with the development and progression of odontogenic tumors, including oncogenes, tumor-suppressor genes, oncoviruses, growth factors, telomerase, cell cycle regulators, apoptosis-related factors, regulators of tooth development, hard tissue-related proteins, cell adhesion molecules, matrix-degrading proteinases, angiogenic factors, and osteolytic cytokines. It is hoped that better understanding of related molecular mechanisms will help to predict the course of odontogenic tumors and lead to the development of new therapeutic concepts for their management.
J Oral Pathol Med (2006) **35**: 65–74

Keywords: molecular alteration; odontogenic tumor

Introduction

Odontogenic tumors are lesions derived from the epithelial and/or mesenchymal elements of the tooth-forming apparatus and are therefore found exclusively within the jawbones (1–3). These development-associated tumors (i) often occur in children or young adults and exhibit considerable histologic variation (Table 1), (ii) are usually intraosseous tumors that contain various amounts of epithelial components and interact with their specific microenvironment, and (iii) are generally benign tumors, but several odontogenic tumors show locally invasive behavior with a high risk of recurrence (1–6).

A series of genetic and molecular alterations appear to promote the development and progression of tumors via multiple steps (7–10). Although the etiology and pathogenesis of odontogenic tumors remain unknown, recent studies have identified various molecular alterations responsible for their development and progression (Table 2). This review provides a contemporary outline of our understanding of the molecular and genetic events associated with odontogenic tumors.

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Accepted for publication August 25, 2005

Molecules involved in tumorigenesis and/or cell differentiation of odontogenic tumors

Oncogenes

Oncogenes are normal cellular genes that contribute to neoplastic transformation by functions activated by gene amplification, translocation, or mutation (11, 12). Many oncogenes have been identified, and their gene products function as growth factors (platelet-derived growth factor (PDGF), fibroblast growth factor (FGF)), growth factor receptors [epidermal growth factor receptor (EGFR), HER-2, Ret], non-receptor tyrosine kinases (Src, Abl), serine/threonine kinases (Mos), signal transducers (Ras), and transcription factors (Myc, Fos). These factors participate in cellular functions related to proliferation and differentiation (11–16).

Ras oncogene was originally characterized on homology studies with rat-transforming gene, and three *Ras* genes, H-*Ras*, K-*Ras*, and N-*Ras*, have been identified in the mammalian genome (15). Products encoded by *Ras* genes, $p21^{Ras}$, are involved in the transduction of external stimuli most likely induced by growth factors (15–17). In ameloblastomas, ameloblastic fibromas, and odontogenic myxomas, $p21^{Ras}$ is expressed preferentially in odontogenic epithelial cells; overexpression of $p21^{Ras}$ is found in odontogenic tumors when compared with normal developing teeth (18). Point mutations of *Ras* genes have been identified in various tumors, including pancreatic, colorectal, bladder, and lung carcinomas (7, 11, 15). A K-*Ras* mutation at codon 12 has been detected in one of 23 ameloblastomas (19).

c-*Myc* oncogene encodes a nuclear phosphoprotein that regulates cellular proliferation (11, 13). Gene amplification and/or protein overexpression of this gene have been identified in many types of tumors (13, 20). In ameloblastomas, c-Myc oncoprotein is expressed predominantly in neoplastic cells neighboring the basement membrane (21). Transgenic mice carrying *Myc* and/or H-*Ras* gene have a high incidence of various odontogenic tumors (22–24).

Table 1 Histologic classification of odontogenic tumors

Benign
Epithelial tumors
Ameloblastoma
Squamous odontogenic tumor
Calcifying epithelial odontogenic tumor (Pindborg tumor)
Adenomatoid odontogenic tumor
Calcifying odontogenic cyst/Odontogenic ghost cell tumor
Mixed tumors
Ameloblastic fibroma/Ameloblastic fibro-odontoma
Odontoameloblastoma
Odontoma
Mesenchymal tumors
Odontogenic fibroma
Odontogenic myxoma
Cementoblastoma
Malignant
Odontogenic carcinomas
Malignant ameloblastoma
Metastasizing ameloblastoma
Ameloblastic carcinoma
Clear cell odontogenic carcinoma
Odontogenic ghost cell carcinoma
Primary intraosseous carcinoma
de novo
cystogenic
Odontogenic sarcomas
Ameloblastic fibrosarcoma
Ameloblastic fibro-odontosarcoma
Odontogenic carcinosarcoma
Related lesions
Cemento-ossifying fibroma
Cemento-osseous dysplasia

Heikinheimo et al. have reported overexpression of *Fos* oncogene, which encodes a transcription factor participating in the control of cell proliferation and differentiation, in ameloblastomas on cDNA microarray and subsequent real-time reverse transcriptase polymerase chain reaction (RT-PCR; 25). These findings suggest that these oncogenes play a role in the pathogenesis of odontogenic tumors via dysregulation of cell proliferation.

Tumor-suppressor genes

Tumor-suppressor genes normally act as regulators of cell growth, and inactivation of these genes by mutations and/or loss of heterozygosity (LOH) in both alleles results in tumor development (11, 26–28). Several tumor-suppressor genes have been identified; *retinoblastoma (RB)*, *p53*, *adenomatous polyposis coli (APC)*, *WT-1*, and *patched (PTC)* genes are well known (27, 28).

p53 gene is one of the most frequently altered genes in tumors, and its gene product plays an important role in response to genomic damage by inducing cell cycle arrest or apoptosis (7, 29, 30). Increased immunohistochemical reactivity for p53 has been detected in ameloblastomas, malignant ameloblastomas, primary intraosseous carcinomas, and ameloblastic fibrosarcomas (31–36), although several studies have shown that *p53* mutations are infrequent in ameloblastomas (34, 36–38). Regulators of p53, MDM2, and $p14^{ARF}$, are also expressed in ameloblastomas, adenomatoid odontogenic tumors, malignant ameloblastomas, and clear cell odontogenic carcinoma; overexpression of MDM2 and $p14^{ARF}$ has been detected in ameloblastomas and malignant odontogenic tumors (34, 36, 39). Recently, p53 homologs, p63 and p73, have been analyzed by immunohistochemistry and RT-PCR, suggesting that these homologs function differently from p53 in odontogenic tissues (40).

APC gene was discovered on genetic analysis of families with familial adenomatous polyposis (FAP), and subsequent studies revealed that its gene product downregulates Wnt signaling pathway, inhibiting cell proliferation (27, 41, 42). While germline *APC* mutations are responsible for FAP, somatic mutations lead to the development of sporadic colorectal tumors (7, 42). Immunohistochemical reactivity for *APC* is lower in benign and malignant ameloblastomas than in tooth germs (43).

Retinoblastoma gene, the first tumor-suppressor gene to be isolated, codes for a nuclear protein controlling

Table 2 Summary of molecules involved in the development and progression of odontogenic tumors

Molecules possibly associated with tumorigenesis and/or tumor cell differentiation	
Oncogenes	*Ras*, *Myc*, *Fos*
Tumor-suppressor genes	*p53*, *APC*
Oncoviruses	HPV, EBV
Growth factors	TGF-α, -β, FGF-1, -2, HGF
Telomerase	Telomerase
Cell cycle regulators	Cyclin D1, $p16^{INK4a}$, $p21^{WAF1/Cip1}$, $p27^{Kip1}$
Apoptosis-related factors	Bcl-2 family, IAP family, Fas, TNF-α, p53
Regulators of tooth development	SHH pathway, Wnt pathway
Hard tissue-related proteins	Amelogenin, Enamelin, Ameloblastin, Enamelysin, BSP, Osteonectin, Osteocalcin, Osteopontin, BMP
Molecules possibly associated with tumor progression	
Cell adhesion molecules	E-selectin, ICAM-1, VCAM-1, E-cadherin, Integrins, CD44
Matrix-degrading proteinases	MMP-1, -2, -9/TIMP-1, -2, Heparanase
Angiogenic factors	VEGF
Osteolytic cytokines	IL-1, -6, TNF-α, PTHrP, RANKL/OPG

HPV, human papilloma virus; EBV, Epstein–Barr virus; TGF, transforming growth factor; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; IAP, inhibitor of apoptosis protein; TNF, tumor necrosis factor; SHH, Sonic hedgehog; BSP, bone sialoprotein; BMP, bone morphogenetic protein; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases; VEGF, vascular endothelial growth factor; IL, interleukin; PTHrP, parathyroid hormone-related protein; RANKL, receptor activator of nuclear factor-κB ligand; OPG, osteoprotegerin.

cell cycle progression together with a transcription factor, E2F (27). Although *RB* has not been investigated in odontogenic tumors, transgenic mice expressing *E2F-1* gene under the control of a keratin 5 promoter have been shown to develop skin tumors and ameloblastomas (44). These features suggest that these tumor-suppressor genes are involved in the development of odontogenic tumors via aberrant control of cell proliferation.

DNA-repair genes

Errors during DNA replication or repair are maintained by DNA-repair genes, such as *MSH2*, *MLH1*, and *PMS1* (45, 46). Aberrations in these genes cause genetic instability, occurring not only in hereditary non-polyposis colorectal cancer (HNPCC) but also in sporadic tumors of the colon, rectum, stomach, pancreas, and endometrium (45–47). In ameloblastomas, representative DNA-repair gene products, MSH2 and MLH1, are immunohistochemically expressed chiefly in peripheral neoplastic cells, suggesting that the development or progression of the odontogenic tumors does not depend on a defect of the DNA maintenance system (48).

Oncoviruses

Many DNA and RNA viruses are oncogenic in a wide variety of animals, and increasing evidence suggests that certain types of human tumors are caused by viruses, such as human papilloma virus (HPV), Epstein–Barr virus (EBV), and human T-cell leukemia virus type 1 (HTLV-1; 49). Approximately 70 genetically distinct types of HPV have been identified, and some types cause squamous papilloma of the skin and squamous cell carcinoma of the cervix and upper respiratory and digestive tracts (49, 50). EBV has been implicated in the pathogenesis of Burkitt lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma, and gastric medullary carcinoma (49, 51, 52). Several investigators have reported HPV and EBV infections in ameloblastomas; however, the etiologic roles of these viruses in odontogenic tumors remain controversial (53–58).

Growth factors

Growth factors are hormone-like polypeptides that play key roles in the control of cell proliferation and differentiation, and many growth factors have been identified, including epidermal (EGF), platelet-derived (PDGF), insulin-like (IGF), hepatocyte (HGF), fibroblastic (FGF), vascular endothelial (VEGF), and transforming (TGF) growth factors (59). Growth factors transmit signals by binding to specific high-affinity cell surface receptors and involving subsequent signaling molecules (17, 60). Dysfunction of growth factors, growth factor receptors, or signaling components results in pathologic conditions, including neoplasia (17, 59, 60).

EGF and TGF-α regulate cell proliferation and functional maturation in a wide range of tissues through their specific receptor, EGFR (59, 61, 62). In tooth germs and various odontogenic tumors, expression of EGF, TGF-α, and EGFR is mostly located in odontogenic epithelial cells (62–64). Odontogenic tumors express TGF-α but not EGF, whereas expression of both EGF and TGF-α has been detected in tooth germs (62). EGFR expression in ameloblastomas is higher than that in epithelial elements of radicular cysts and granulomas (63). These features suggest that TGF-α and EGFR are involved in odontogenic tumorigenesis.

TGF-β is a multifunctional growth factor involved in the control of cell growth, cell differentiation, cell migration, and the synthesis and degradation of extracellular matrix (59, 60). TGF-β and its receptors (TGF-β receptor types I and II) are expressed in many types of odontogenic tumors, suggesting that they have an important role in cell differentiation and matrix formation via regulation or dysregulation of epithelial–mesenchymal interactions (65–68).

HGF has mitogenic, motogenic, and morphogenic functions in various types of cells and acts via its receptor, c-Met (69). This growth factor is essential for morphogenesis of tooth germs (70). HGF and c-Met are expressed in many types of odontogenic tumors, suggesting that they affect epithelial–mesenchymal interactions not only in developing teeth but also in neoplastic odontogenic tissues (67, 68). Increased expression of HGF and c-Met in ameloblastic carcinomas and clear cell odontogenic carcinomas implies that HGF signaling might be associated with the malignant potential of epithelial odontogenic tumors (67).

FGF is widely distributed and functions in the growth, differentiation, and regeneration of a variety of tissues (71). Several types of FGF are also involved in tooth formation (72, 73). Expression of FGF-1, -2, and their types 2 and 3 receptors has been detected in various odontogenic tumors, suggesting that these molecules are associated with odontogenic differentiation rather than pathogenesis (74, 75).

Ras/MAPK and PI3K/Akt pathways function downstream to growth factor receptors and regulate cell proliferation and differentiation (15, 17). Alterations of involved signaling molecules have been identified in a variety of human tumors (17, 76, 77). In ameloblastomas, Ras/MAPK and PI3K/Akt pathways have been examined, but no distinct aberrations of the signaling molecules have been detected (19, 78).

Telomerase

Telomerase is a specialized reverse transcriptase that synthesizes telomeric DNA at the ends of chromosomes and compensates for its loss with each cell division, participating in cell immortalization (79). Activation of telomerase has been demonstrated in most human malignancies (79, 80). On telomeric repeat amplification protocol (TRAP) assay, ameloblastoma tissues have been consistently positive for telomerase activity, suggesting that telomerase activation is associated with tumorigenesis of odontogenic epithelium (21, 81). Immunohistochemical reactivity for telomerase in ameloblastomas shows a similar distribution pattern to that of c-Myc protein, an oncogene product that directly activates telomerase transcription, suggesting that this oncoprotein induces telomerase activity in ameloblastomas (21).

Cell cycle regulators

Cell proliferation follows an orderly progression through the cell cycle, which is governed by numerous factors, including cyclins, cyclin-dependent kinases (CDKs), CDK inhibitors (CKIs), and other critical regulators (82, 83). Uncontrolled cell cycles caused by aberrations of these regulators have been identified in a variety of tumors (82, 84). In many types of odontogenic tumors, cell cycle phase/cell proliferation markers, proliferating cell nuclear antigen (PCNA), Ki-67, DNA topoisomerase IIα, and histone H3, reflect proliferation activity and malignant potential (31, 33, 68, 85–92). Cyclin D1 is strongly implicated in cell cycle progression by regulating the transition from G1 to S phase, while CKIs, $p16^{INK4a}$, $p21^{WAF1/Cip1}$, and $p27^{Kip1}$ inhibit cell cycle progression by suppressing cyclin D1 function (83). In ameloblastomas, expression of cyclin D1, $p16^{INK4a}$, $p21^{WAF1/Cip1}$, and $p27^{Kip1}$ is well preserved when compared with tooth germs, suggesting that the proliferation of odontogenic epithelial cells is strictly controlled by these cell cycle regulators (91).

Apoptosis-related factors

Apoptosis, also known as programmed cell death or physiologic cell death, has diverse roles in embryogenesis and normal homeostasis, as well as in a variety of pathologic conditions (93, 94). There are two alternative apoptotic pathways, one mediated by death receptors and the other by mitochondria, and apoptotic processes are modulated by a large family of genes, such as the tumor necrosis factor (TNF) family, the Bcl-2 family, and the inhibitor of apoptosis protein (IAP) family (95–100). Evasion from apoptosis by aberrations of apoptosis regulatory factors has been found to cause the accumulation of neoplastic cells in various tumors (94–96, 98).

In some epithelial odontogenic tumors, apoptotic cells have been detected by TdT-mediated dUTP-biotin nick end-labeling (TUNEL) and immunohistochemistry using single-stranded DNA (ssDNA) antibody, suggesting that apoptotic cell death plays an important role in oncogenesis and cell differentiation in odontogenic epithelium (33, 101–104). Representative death receptors, Fas, TNF receptor I (TNFRI), and TNF-related apoptosis-related ligand (TRAIL) receptors 1 and 2, have been recognized in benign and malignant ameloblastomas, but expression of caspase-8, an apoptosis initiator in the death receptor-mediated apoptotic pathway, is extremely limited, suggesting that apoptotic cell death in odontogenic epithelial components is minimally affected by signaling of death factors (103, 105). Although the apoptosis signaling pathway mediated by mitochondria has not been investigated in odontogenic tumors, Bcl-2 and IAP family proteins, modulators of the mitochondrial apoptotic pathway, have been examined in various types of odontogenic tumors. In these odontogenic tumors, apoptosis inhibitory factors, such as Bcl-2, Bcl-x, survivin, and X chromosome-linked IAP (XIAP), are predominantly expressed, suggesting that these apoptosis modulators are associated with survival and neoplastic transformation of odontogenic epithelial cells (33, 68, 88, 92, 102, 104, 106–110).

p53, a tumor-suppressor gene product, induces apoptosis if DNA has suffered irreversible damage (29, 111). In ameloblastomas, p53 expression has been detected, but the association between p53 and apoptosis remains uncertain (31, 33).

Regulators of tooth development

Tooth development is under the strict genetic control of regulators that determine the positions and shapes of the teeth, such as Msx-1, Msx-2, Dlx-2, Barx-1, and Pax-9, or that are involved in the morphogenesis and cytodifferentiation of the teeth, such as Sonic hedgehog (SHH), bone morphogenetic protein (BMP), Wnt, HGF, and FGF (112, 113). Aberrant functions of these specific genes cause various dental anomalies (114, 115).

SHH signals control cell–cell interactions and cell proliferation in tissue patterning of various organs, including the teeth (116, 117). *Patched (PTC)*, whose product is one of the SHH signal transduction molecules, is responsible for basal cell nevus syndrome (BCNS), characterized by basal cell carcinomas and odontogenic keratocysts (118, 119), and mutations of *PTC* have been identified in both BCNS-associated and sporadic odontogenic keratocysts (120, 121). On cDNA microarray, ameloblastomas show underexpression of SHH and PTC (25). Expression of SHH signaling molecules, SHH, PTC, smoothened (SMO), and GLI1, has been detected in several odontogenic tumors (122, 123). These findings suggest that SHH signaling pathway plays a role in epithelial–mesenchymal interactions and cell proliferation during the growth of odontogenic tumors as well as during tooth development.

Wnt signal transduction controls diverse developmental processes by regulating cell proliferation, morphology, motility, and fate in various organs, including the teeth (41, 124). Mice targeted for the Wnt signaling molecule *LEF-1* show inhibition of tooth morphogenesis (125). Wnt signaling is regulated by the levels of β-catenin, and activation of this pathway results in cytoplasmic accumulation and nuclear translocation of β-catenin (41). Mutations of *β-catenin* are detected frequently in calcifying odontogenic cysts, but are rare in ameloblastomas (126). Nuclear expression of β-catenin protein has been found in calcifying odontogenic cysts and benign and malignant ameloblastomas (43, 126, 127). APC, a product of tumor-suppressor gene, downregulates Wnt signaling pathway by inducing β-catenin degradation (41, 42), and immunohistochemical reactivity for APC is low in benign and malignant ameloblastomas (43). These findings suggest that aberrations of Wnt signaling pathway are involved in oncogenesis and cytodifferentiation of odontogenic epithelium via dysregulation of cell proliferation.

Other regulators of tooth development, such as HGF and FGF, have been found in odontogenic tumors (67, 68, 74, 75).

Hard tissue-related proteins

Enamel matrix is made from non-collagenous proteins and contains enamel proteins, such as amelogenin,

enamelin, ameloblastin (amelin or sheathlin), and tuftelin, and enzymes, such as matrix metalloproteinase (MMP)-20 (enamelysin) and enamel matrix serine proteinase 1 (128). Genetic alterations of enamel proteins have been implicated in various subtypes of amelogenesis imperfecta, a group of disorders that solely affect enamel formation (129, 130). Expression of amelogenin, enamelin, ameloblastin, and MMP-20 has been recognized in epithelial components of various types of odontogenic tumors (68, 92, 131–139). Recently, mutations of *ameloblastin* gene have been detected in ameloblastomas, adenomatoid odontogenic tumor and squamous odontogenic tumor (138, 140), and *ameloblastin*-mutant mice develop odontogenic tumors of odontogenic epithelium origin (141). These findings suggest that aberrations of enamel-related proteins are involved in oncogenesis of odontogenic epithelium.

Mineralized matrices of dentin, cementum, and bone contain type I collagen and numerous non-collagenous proteins, such as bone sialoprotein (BSP), osteonectin, osteocalcin, osteopontin, and dentin matrix protein 1 (DMP1; 142, 143). Two dentin proteins, dentin sialoprotein (DSP) and dentin phosphoprotein (DPP), are tooth-specific (144). Recent studies suggest that DSP, DPP, or DMP1 may cause dentinogenesis imperfecta type II, a hereditary developmental disturbance of dentin without any systemic disorder (129). BSP, osteonectin, osteocalcin, and osteopontin are found in many types of odontogenic tumors, suggesting that these proteins play a role in pathologic mineralization and/or tumor formation (134, 145–147). Furthermore, expression of BMP, which induces bone and cartilage formation, has been recognized in mixed and mesenchymal odontogenic tumors but not in epithelial odontogenic tumors (148).

Molecules involved in progression of odontogenic tumors

Cell adhesion molecules

Cells are neatly glued to each other and their surroundings by a variety of cell adhesion molecules, and aberrations in such interactions can lead to pathologic conditions (10, 149). Invasion and metastasis of various neoplastic lesions have been reported to correlate with altered adhesive systems involving cell adhesion molecules, such as E-cadherin, E-selectin, integrins, and CD44 (10, 150–152).

Vascular endothelium cell adhesion molecules, such as E-selectin, intercellular adhesion molecule (ICAM)-1, and vascular cell adhesion molecule (VCAM)-1, mediate leukocyte adhesion in inflammatory processes (153). Ameloblastomas express these cell adhesion molecules in vascular endothelium, suggesting that stromal blood vessels are activated in the odontogenic tumors (154). A major cell adhesion molecule for homophilic cell–cell adhesion of epithelial cells, E-cadherin, and its undercoat protein, *alpha*-catenin, are found in epithelial odontogenic tumors, and a case of malignant ameloblastoma has shown markedly decreased expression of these molecules (155). Integrins and CD44 mediate cell–cell and cell–extracellular matrix adhesion in various tissues (150, 151). Ameloblastomas have shown expression of several integrins and CD44 predominantly at epithelial–mesenchymal interfaces, suggesting that these cell adhesion molecules might mediate parenchymal–stromal interactions in the odontogenic tumors (156, 157).

Matrix-degrading proteinases

Extracellular matrix degradation occurring during developmental processes, tissue remodeling, inflammatory diseases, and tumor progression requires the action of proteolytic enzymes, such as MMPs and matrix serine proteinases (MSPs) (9, 10, 158). Extracellular matrix components, such as collagens, fibronectin, tenascin, laminin, and proteoglycans, have been detected in various odontogenic tumors (134, 159–164). Ameloblastomas and odontogenic myxomas express MMPs-1, -2, and -9, which degrade extracellular matrix and basement membrane components, and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs)-1 and -2, have also been recognized in ameloblastomas (108, 165, 166). Recently, expression of heparanase, which cleaves proteoglycans, has been detected in ameloblastomas (167). These features suggest that matrix-degrading enzymes may contribute to the local invasiveness of odontogenic tumors.

Angiogenic factors

Angiogenesis is an essential part of a variety of physiologic and pathologic processes, including embryogenesis, wound healing, inflammation, and tumor progression, and these processes are controlled by numerous different molecules, such as VEGF, FGF, HGF, TGF-β, interleukin (IL)-8, and TNF-α (168–170). Immunohistochemical evaluation of microvessel density by means of the vascular endothelial marker CD34 has shown higher vascularity in benign and malignant ameloblastomas than in tooth germs. Simultaneously, increased expression of VEGF, which enhances angiogenesis and vascular permeability, has been found in these odontogenic tumors (171). These features suggest that VEGF is an important mediator of tumor angiogenesis in ameloblastic tumors, and upregulation of VEGF might be associated with tumorigenesis or malignant transformation of odontogenic epithelium.

Osteolytic cytokines

The integrity of bone metabolism is maintained by a delicate balance between bone formation by osteoblasts and bone resorption by osteoclasts, and its dynamics is regulated by a wide variety of hormones, growth factors, and cytokines (172, 173). Inflammatory cytokines with osteolytic activity, such as IL-1, IL-6, and TNF-α, are synthesized in ameloblastomas (105, 154, 174, 175).

Hypercalcemia is the most common metabolic complication of malignancy, and parathyroid hormone-related protein (PTHrP) has been implicated in malignancy-associated hypercalcemia (173, 174, 176, 177). This peptide shows structural and functional homology with PTH and increases osteoclastic bone

resorption and renal tubular calcium reabsorption (177). Several cases of malignant ameloblastoma with hypercalcemia have been attributed to PTHrP (178, 179), and expression of PTHrP has been detected in neoplastic cells of benign and malignant ameloblastomas unassociated with hypercalcemia (180, 181).

Receptor activator of nuclear factor-κB ligand (RANKL) binds to its receptor expressed on osteoclast precursors, RANK, and stimulates osteoclast differentiation and activation, while osteoprotegerin (OPG) functions as a decoy receptor for RANKL and inhibits osteoclastogenesis and osteoclast activation (172). The balance between RANKL and OPG levels regulates osteoclasts and bone metabolism, and abnormalities of the RANKL–OPG system have been implicated in the pathogenesis of various bone lesions (172, 173). Benign and malignant ameloblastomas express RANKL and OPG predominantly in stromal cells rather than tumor cells (181, 182). These observations suggest that osteolytic cytokines have a role in local bone resorption during the progression of odontogenic tumors.

Concluding remarks

The development and progression of odontogenic tumors are affected by alterations of many kinds of genes and molecules. In particular, the characteristics of odontogenic tumors appear to depend on the molecular mechanisms associated with (i) tooth development, (ii) bone metabolism, and (iii) the malignant potential of tumors. Further molecular studies, including genomic- and proteomic-based profiling, are required to clarify the etiology and pathogenesis of odontogenic tumors. A better understanding of underlying molecular mechanisms will help to predict the course of odontogenic tumors and lead to the development of new therapeutic applications, such as molecular-targeted treatment and patient-tailored therapy, for odontogenic tumors.

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