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REVIEW

New diagnostic molecular markers and biomarkers in odontogenic tumors

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Abstract

Odontogenic tumors comprised of complex heterogeneous lesions that diverse from harmatomas to malignant tumors with different behavior and histology. The etiology of odontogenic tumors is not exactly determined and pathologists deal with challenges in diagnosis of odontogenic tumors because they are rare and obtained experiences are difficult to evaluate. In this study, we describe immunohistochemical and molecular markers in diagnosis of odontogenic tumors besides advanced diagnostic technique. Immunohistochemical features of odontogenic tumors beside the clinical features and radiological finding can help us to determine the correct diagnosis. Although these markers are neither specific nor sensitive enough, but analysis of gene expression provides definitive confirmation of diagnosis. In addition, "-omics" technology detected specific molecular alternation associated with etiology such as genomics, epigenomics, transcriptomics, proteomics and metabolomics. The post transcriptional events such as DNA methylation and chromatin remodeling by histone modification affect the changes in epigenome. Furthermore, non-coding RNAs like micro-RNAs, long noncoding RNA (lncRNA) and small non-coding RNA (snoRNA) play regulatory role and impact odontogenesis. Molecular marker propose their potential role in etiopathogenesis of odontogenic tumors and suitable candidate in diagnostic, prognostic and therapeutic approaches in addition to patient management. For future evaluations, organoid represents in vitro tumor model-study for tumor behavior, metastasis and invasion, drug screening, immunotherapy, clinical trial, hallmarks association with prognosis and evolution of personalized anti-cancer therapy. Moreover, organoid biobank help us to check genetic profile. We think more investigation and studies are needed to gain these knowledges that can shift therapeutic approaches to target therapy.

Keywords Odontogenic tumor · Immunohistochemistry · Molecular marker · Biomarker · Oral lesions

Introduction

Odontogenic tumors comprise of complex heterogeneous lesions that originate from ectomesenchymal and/or epithelial odontogenic tissues and manifest following normal tooth development. They are diverse from harmatomas to malignant tumors with different behavior, histology and even different geographical distribution [1]. The odontogenic tumors manifest variant clinical features including disfigurement of the face, jaw expansion and extension, root and bone resorptions, teeth mobility and alternation in bone density [2]. There are two primary classification for odontogenic tumors including benign odontogenic tumors that arise de novo and malignant odontogenic tumors that almost take from benign precursor, but WHO categorized the new edition based on origin of tissue and histological characteristics in 2017 that are mentioned in Table 1 [3, 4]. It was reported that among all oral tumors, odontogenic tumors are less than 1%, and also 99.2% of them are benign type [5].

Markers are molecules, genes or molecular features in pathogenesis of disease play a critical role in diagnosis and management of patients, especially in tumorigenic cases [6]. It was identified a few markers for evaluation of odontogenic tumor s pathogenesis, but immunohistochemistry (IHC) may be useful for pathologists. Although histological features of odontogenic tumor such as morphology along with

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Table 1 The last WHO classification of odontogenic tumors (2017) with diagnose and prognoses features

Odontogenic tumor	Clinical feature	Histopathologic feature	Differential diagnosis	Prognosis and treatment
Odontogenic carcinoma				
Ameloblastic carcinoma	Irregular marginated radiolucency. cortical expansion, perforation and infiltration into adjacent structures	Histological characters of malignancy in ameloblastoma	- Any odontogenic tumor with ameloblastic differentiation	- In 1/3 of patient metastasis to pulmonary - Most survival age is ~ 5 years - primary treatment: radical surgical excision - aggressive multimodality from the outset
Primary intraosseous carcinoma (PIOC), NOS	Slow growing of, pain, ulceration, loosening of teeth, non-healing extraction socket, and pathological fracture and nerve signs	small nest of neoplastic squamous without prominent keratinization	Squamous odontogenic tumors,intra osseous mucoepidermoid carcinoma,primary jaw SCC	- best predicted by histological grade - primary treatment: radical resection with neck dissection or for metastasis or reconstruction - multimodality treatment
Sclerosing odontogenic carcinoma (SOC)	Swelling, sometimes with nerve sign, sinus involvement	Single-file thin cords, nests and strands of epithelium in a densely sclerotic stroma	- Calcifying epithelial odontogenic tumor - Desmoplastic ameloblastoma	- Main treatment: resection
Clear cell odontogenic carcinoma	Almost are asymptomatic	Lobular sheets or islands composed of clear to faintly eosinophilic cytoplasm	Pindborg tumor (clear cell type), intra osseous mucoepidermoid carcinoma	- Variant behavior from indolent tumors to cases that frequently recur - Complete surgical resection
Ghost cell odontogenic carcinoma (GCOC)	Slow growing, swelling of the jaw, pain, ulceration, loosing of teeth, nerve signs, root resorption and sometimes soft tissue invasion	cytological evidences of malignancy associated with ghost cells, dentinoid formation		from slow growing, locally invasive carcinomas to highly aggressive and rapidly growing tumors with local recurrence and metastasis
Odontogenic carcinosarcoma				
Odontogenic sarcomas				
Benign epithelial odontogenic tumors				
Ameloblastoma:	Slow and painless loosening of teeth, paraesthesia, pain, soft tissue invasion, facial deformity, limited mouth opening	Ameloblastic differentiation,reverse polarity and central loosely arranged, stellate cells	- Any odontogenic lesion with ameloblastic differentiation	- Current treatment: surgical excision - New therapeutic approach based on *BRAF* targeting complement surgery
Ameloblastoma, unicystic type (UAM)	- Asymptomatic painless jaw expansion - Unilocular radiolucency	- Luminal, intraluminal types	odontogenic cysts - benign odontogenic tumors	- Initial treatment: enucleation - Further treatment is determined by pattern and extend of the ameloblastomatous proliferation
Ameloblastoma, extraosseous/peripheral type	- Painless, sessile, exophytic lesion	ameloblastic differentiation,reverse polarity and central loosely arranged, stellate cells	- Peripheral odontogenic lesions - Reactive lesins	- Conservative removal with free margins is expected to be curative - Recurrence is rare, but long tem follow up is warranted
Metastasizing ameloblastoma	- More determined by clinical behavior - Diagnosis made only in retrospect after occurrence of metastasis	Histological features of primary and metastasizing are similar	- Conventional solid or multicystic ameloblastoma	- The overall 5-year survival rate is depend on the site of metastasis and surgical accessibility

Table 1 (continued)

Odontogenic tumor	Clinical feature	Histopathologic feature	Differential diagnosis	Prognosis and treatment
Squamous odontogenic tumor (SOT)	- Asymptomatic - Tumor grow slowly with bone expansion - Unilocular radiolucency	Differentiated squamous epithelium of varying shape and size cell keratinization	- Acanthomatous Ameloblastoma -desmoplastic variants -squamous cell carcinoma	- Remove by surgery - Recurrence is rare
Classify epithelial odontogenic tumor (CEOT)	grows slowly with bone expansion - Unilocular or multiocular mixed radiolucency	islands, cords and sheets of neoplastic polyhedral epithelial cells with relative pleomorphism, liesegang rings, without prominent mitotic activity	- Primary intraosseous squamous cell carcinoma -Central mucoepidermoid carcinoma, metastatic renal cell carcinoma, clear cell odontogenic carcinoma	- most cases treated with local surgical removal - recurrence rate is about 15%
Adenomatiod odontogenic tumor (AOT)	- Limit growth but many hamartomas - symptomatic with/without bony expansion - small loci of radiopacity	- encapsulated spindled epithelial cells, Rossette or duct like spaces, - Eosinophilic material within tumor like secretion product	- Odontoma - Ameloblastoma Classifying epithelial odontogenic tumor	- They are encapsulated and envariably enucleated - Recurrence rates are exceeding low
Benign mixed epithelial and mesenchymal odontogenic tumors				
Ameloblastic fibroma (AF)	- Slow growing, painless - Unilocular radiolucency, multicular related to larger lesions	- Mesenchymal component: myxoid, cell-rich and resembled the dental papilla of the tooth bud - Epithelial component: pattern of narrow, elongated strands of two tight and parallel-running with budding, layers of cuboidal to columnar cell or assembled follicular stage of enamel	- Early stage odontoma -Early stageAmeloblastic fibroodontoma - Ameloblastoma	- Small, asymptomatic tumors (especially in young children) are removed conservatively; however, ulteraconservative treatment might result in recurrence - Extensive, destructive tumors treated radically
Primordial odontogenic tumor	- An unerupted tooth (most commonly the lower third molar) with apparent pericoronal relationship on radiographical image - Most asymptomatic	loose fibrous tissue with variant fusiform and stellate fibroblast and peripheral columnar/cuboidal epithelium	- Odontogenic myxoma - Ameloblastic fibroma - Centeral odontogenic fibroma	- local excision - no recurrence until 20 years

Table 1 (continued)

Odontogenic tumor	Clinical feature	Histopathologic feature	Differential diagnosis	Prognosis and treatment
Odontoma: Odontoma, compound type Odontoma, complex type	- Related to unerupted tooth and detectable in radiographs - Asymptomatic but may inflamed during trauma or eruption - Well-demarcated radiopacity surrounded by a thin soft tissue capsule and an adjacent corticated layer of bone - Radiological features: Compound type: diagnostic, many tooth-like structures. complex type: disorganized mass of classified tissues might indistinguish from other classified bone lesions	- Compound type: multiple rudimentary teeth demonstrating dentin, cementum, enamel matrix, pulp and adjacent fibrous with dental follicle - Complex type: tubular dentin enclosed zones of enamel matrix, decreased enamel epithelium with infrequent scattered ghost cell - A narrow layer of cementum in peripheral of mass	- Ameloblastic fibroma -Odontoameloblastoma	- Remove by conservative surgery if be low growth - Prognosis is excellent
Dentinogenic ghost cell tumor (DGCT)	- cortical bone expansion - unilocular or multilocular radiolucency radiolucent,mixed or radiopaque, well defined border	- Odontogenic epithelium with areas closely resembling ameloblastoma - Presence of ghost cells: Abberant keratinization with calcification	Ameloblastoma with ghost cell	- recommended treatment: segmental surgury - Conservative surgery (enucleation, curettage/simple excision), rate of recurrence: 73% until 20 years - radical surgery: marginal/segmental resection, rate of recurrence: 33% more than 1 years
Benign mesenchymal odontogenic tumors				
Odontogenic fibroma	asymptomatic, but large with pain, bony expansion, - Radiological features uniocular or multiocular - corticated margin	cellular or collagenous connective tissue with varying amounts of inactive-looking odontogenic epithelial islandshard tissue formation may observed	desmoplastic fibroma, Odontogenic myxoma, desmoplastic ameloblastoma, ameloblastic fibroma,—peripheral odontogenic fibroma: peripheral	- Treat of central odontogenic fibroma: enucleation, curettage,and need removal of adjacent involved teeth - Treat of peripheral odontogenic fibroma: surgical excision, extend down to periosteum Recurrence rate is 50%
Odontogenic myxoma/myxofibroma	- Slow, painless expansion - Early lesion are unilocular radiolucency but following enlargement become multilocular - Well-defined margin on radiographs - Soap-bubble or cubweb shape	- Resemble to dental papilla and follicle of the developing tooth - Proliferation of spindle-shaped to stellate fibroblast in back ground	- Primordial odontogenic myxoma - Centeral myxoid neurofibroma - Chondromyxoid fibroma - Myxoid chondrosarcoma	Small lesion: curtage, large lesion: en bloc or segmental resection Recurrence in ¼ of ceses with conservative therapy following incomplete exision

Table 1 (continued)

Odontogenic tumor	Clinical feature	Histopathologic feature	Differential diagnosis	Prognosis and treatment
Cementoblastoma	- > 60% cases with pain or swelling Radiopaque mass with surrounding radiolucent rim fused to the apex of a tooth, usually the mandibular first molar (50%) or a premolar - Teeth are generally vital	Proliferation of cementoblasts (large, eccentric nuclei (slightly atypical) with dispersed chromatin and small nucleoli similar to osteoblasts), which deposit cementum (osteoid-like), woven bone-like material in masses Resting and reversal lines are often present, and the attached root may be resorbed	- Osteoblastoma - Cementoosseous dysplasia - Hypercementosis - Osteosarcoma	- Excision or resection of the tumor with the tooth - 10–20% rate of recurrence
Cemento-ossifying fibroma (COFs)	In tooth bearing areas of the jaws with odontogenic origin Painless expansion of buccal and lingual plates of the affected bone Large lesions expand the inferior border of mandible or floor of the maxillary sinus More radiopaque over time	Encapsulated Hyper cellular fibroblastic stoma and variable amount of calcified structure Osteoblastic rimming of the bone trabeculae	- Cemento-osseous dysplasia - Fibrous dysplasia	A slow grow benign neoplasm Excited by conservative surgical No recurrence in most cases

radiology provide clinical diagnosis, but cystic lesions, tiny biopsies and determination of malignancy changes are some problems [7]. Also, over/under expression of some genes are reported as molecular marker in odontogenic tumors [8]. In this manner, specific markers help us in the correct diagnosis of special types of odontogenic tumor, and it increases our knowledge about pathogenesis and molecular genetic features of these lesions. In this study, we describe immunohistochemical and molecular markers in diagnosis of odontogenic tumors and investigate recent studies based on "omics" that provide more information about prognosis and therapeutic approach of these tumors in addition to diagnosis.

Diagnostic markers in odontogenic tumors

Immunohistochemical markers in diagnosis of odontogenic tumors

Immunohistochemistry (IHC) is an immunostaining technique that detected antigens (proteins) by binding antibodies in cells or tissue. The main benefit of IHC is detection of a specific target following antibody-antigen interaction and can apply in diagnosis of cancerous tumor subsequent to proliferation or cell death. In addition, location and distribution of expressed protein are emerged in various parts of tissue. For instance, it was reported significant expression of podoplanin in invasive odontogenic tumors by immunohistochemistry technique that emphasized the diagnostic role of this marker on neoplastic behavior [9]. Also, overexpression of MDM2 and p53 was demonstrated in solid multicystic ameloblastoma (SMA) and keratocystic odontogenic tumor (KOT) as IHC markers [10]. In addition, histological features of the lesion can be helpful in differential diagnosis of rare extension cases such as calcifying epithelial odontogenic tumor (CEOT) or Pind-borg tumor that expand to the maxillary sinus [11]. The high expression of Cripto-1 or teratoma-derived growth factor 1 (TDGF-1) in almost of aggressive odontogenic lesions proposed involvement of this molecules in ethiopathogenesis [12].

So, IHC seems to be useful for evaluation of tumors by molecular biomarkers. In this manner, Immunohistochemical features of odontogenic tumors beside the clinical features and radiological finding can help us to determine the correct diagnosis. Because the correct diagnosis helps us for better patient management in therapy. Some side effects of radiotherapy for head and neck cancers include xerostomia, dental caries and oral ulcers that affect oral intake and difficulty in speech. Moreover, radiotherapy increases osteosarcoma and oral infection like *oral candidiasis* because stomach reflex manifests following nausea and vomiting [13]. So, biomarker diagnosis plays a critical role in patient management. There are restricted studies to share results of

diagnostic proteins in odontogenic tumors, and some of them are mentioned in Table 2 [14, 15].

Potential molecular markers in diagnosis of odontogenic tumors

The etiology of odontogenic tumors is not exactly determined, but the result of next-generation sequencing demonstrated specific mutation improved the biology process in tumorigenesis of odontogenic tumors. They involve in cell proliferation and differentiation, control of cell cycle, regulation of tooth development or be growth factor and receptors, telomerase, apoptotic factors and extracellular matrix remodeling [16]. Most of them that involve in the molecular pathogenesis of odontogenic tumors are oncogene or tumor suppressor genes that we mentioned in Table 3 [17–19]. On the other hand, post transcriptional events such as methylation influences gene activity without any changes in DNA sequence. In this manner, DNA methylation and chromatin remodeling by histone modification inhibit recruitment of splicing or transcription factors. So imprinting or suppress of gene expression result in tumor development [20]. Thus, the tumor biology is affected by the changes in the genome and epigenome.

In addition, some non-coding RNAs like micro-RNAs—small noncoding RNA with 21–25 nt—have regulatory role and impact odontogenesis. For example, miR-16–1 and miR-15a play tumor suppressor role by repression of *BCL-2* gene and induce apoptosis. It was shown that the expression of *BCL-2* is increased in KOT, but the expression of mir-16–1 and mir-15a are reduced [21]. Profile of micro-RNA expression emerged 40 micro-RNAs with different expression in ameloblastoma compare to control group [22].

Long-noncoding RNA (lncRNA) is another regulatory molecule—more than 200 nt in length—that participates in chromatin modulation and affects transcription and translation [23]. Result of RNA microarray analysis demonstrated LINC-340 up regulated in ameloblastoma and associated with the size of the tumor [24]. Furthermore, another class of small non-coding RNA (snoRNA) that modified ribosomal RNA positively correlated to size of tumor such as SNORA11 in ameloblastoma [24]. This significant different expression of the molecular marker proposes potential role of them in etiopathogenesis of odontogenic tumors and suitable candidate in diagnostic and therapeutic approaches.

In recent years "-omics" studies discover potential candidate biomolecules in pathogenesis of odontogenic lesions [19]. "-omics" technology provides comprehensive biological information that analyses specific types of molecules. For example, genomics, epigenomics, transcriptomics, proteomics and metabolomics are different levels of this technology that evaluates alterations in DNA, non-DNA sequence, RNA, proteins and metabolites, respectively (Fig. 1) [25]. This technology enables to detect molecular mechanism, etiology, for better management of affected odontogenic patients. In this regard, some studies exhibit the result of "-omics" in odontogenic cases that can apply in diagnostic approaches [19]. For example, protein plays a regulatory role during cell function and because of dynamic protein interaction in a complex, proteomics-based technology provides identification and quantification of proteome. So it will be applicable in diagnostic approaches in addition to prognosis and therapeutic to vaccine development [26]. In odontogenic tumors, proteomics emerged significant alternation of protein levels in some classified types. For instance, it was reported the increasing level of AIDA protein in odontogenic keratocyst [27].

Understand of molecular pathology helps us to develop a therapeutic approach in addition to diagnosis. For instance, immunostaining of ameloblastoma cases demonstrated p53 and MDM2 was high in odontogenic keratocyst (OKC) followed by solid multicystic ameloblastoma (SMA) [10]. Also, immunoexpression of PTEN in ameloblastoma cases showed significant reduction in immunoactivity [28].

Discussion

The pathologists deal with challenges in diagnosis of odontogenic tumors because they are rare and obtained experiences are difficult to be evaluated. The diagnosis is determined based on morphology, clinical manifestation and radiological features, but the outcome of many studies demonstrated immune-histochemical marker can help us to diagnose of some odontogenic tumors. Although these markers are neither specific nor sensitive enough, but analysis of gene expression can help us in definitive confirmation of diagnosis. Based on the molecular pathway that lesions are involved, expression of some genes changes as overexpression or aberrant expression. In addition, "-omics" technology detected specific molecular alternation associated with etiology of disease. But low frequency of odontogenic lesions restricted researches to discover many aspects of disease. Whole genome sequencing and transcriptomics in ghost cell odontogenic carcinoma manifested involving of NOTCH and SHH pathways including increased copy number of *SHH*, *GLI1*, *JAG1*, *DTX3*, and *HEY1* that result in overexpression of them. Furthermore, fusion of *TCF4* and *PTPRG* genes defect tumor suppressor activity of tyrosine phosphatase receptor type G protein [29].

Understand of odontogenic pathogenesis of odontogenic tumors assistances with diagnosis of malignant transformation, development and progression of lesions. It seems if that tissue samples after collection embedded in paraffin or formalin-fixed can be saved as a bio bank for future evaluation. Recent technologies provide easy access to

Table 2 Summery of immune-histochemical odontogenic tumor markers

Marker	Function	Diagnostic marker
Cytokeratin (CK)	An intermediate filament (structural cytoskeleton protein)	- Odontogenic tumors with epithelial origin express CK14 and CK19 - AOTs express CK 5, 14, 19 - Ameloblastoma express CK 5, 14, 19, 56 - Clear cell odontogenic carcinoma express CK5, 6, 14, 19 and pancytokeratin AE1/AE3 - Primordial odontogenic tumor strongly positive for CK5, 14 and pancytokeratin AE1/AE3 - DGCT epithelial cells express CK5, 7, 14, 19 - CEOT express CK5, 6 - Odontogenic fibroma positive for AE1/3, K8/18, K14, and K19
Amelogenin	Enamel matrix protein that organize enamel rods and mineralize enamel	- Express in odontogenic tumors with epithelial origin such as ameloblastoma, AOT, CEOT, AF, malignant ameloblastoma and ameloblastic carcinoma
Ameloblastin (AMBN)	A cell adhesion molecule that inhibit ameloblasts proliferation	Ameloblastoma, AOT, SOT, CEOT
Calretinin (calbindin-2)	A calcium-binding protein that modulate intra cellular Ca^{++} ion	- Express in solid and unicystic ameloblastomas
Bone morphogenetic proteins (BMPs)	Play role in cell proliferation, differentiation, chemotaxis, extracellular matrix production, apoptosis and mesenchymal cell differentiation formation of calcified dental tissues and odontogenic tumor development	- Express in epithelial odontogenic tumors such as ameloblastomas and adenomatoid odontogenic tumor
Tenascin	A glycoprotein play role in cell–cell and cell-extracellular matrix interactions	- Form calcifying mass in CEOT, ameloblastic fibro-odontoma (AFO) and odontoma
Nestin	A intermediate filament (structural cytoskeleton protein)	- Odontogenic ectomesenchyme in mixed tumours such as AF, AFO, ameloblastic fibrodentinoma (AFD) and ameloblastic fibrosarcoma (AFS)
High-mobility group A protein 2 (HMGA2)	Non-histone chromatin factor	- Over express in odontogenic mesenchymal tumors such as OM, odontogenic myxofibroma
Basement membrane proteins	Distinction of extracellular matrix (ECM) and epithelium, adjacent connective tissue stroma	- Express in odontogenic tumors epithelium such as laminin
Cytoskeleton remodeling protein (moesin and RhoA)	Connect the plasma membrane and cytoskeleton with maintaining and remodeling them	- Strongly express in odontogenic epithelial cells and involvement in development of benign odontogenic lesions
Vimentin	A intermediate filament (structural cytoskeleton protein)	- Express in mesenchymal cell of primordial odontogenic tumor, central odontogenic fibroma
CD138 (syndecan-1) and MMP9	CD138: A heparin sulphate proteoglycan controls tumor cell growth, adhesion and differentiation MMP9: involved in the degradation of the extracellular matrix	- Express in tumor and stromal cell of DGCT
Calretinin	Play role in message targeting and intracellular calcium buffering	Ameloblastoma
CD68, lysozyme	Present with macrophage, lysis	central odontogenic fibroma
S100	A family of calcium-binding proteins	Odontogenic myxoma
Ki-67	Cell proliferation marker	Ameloblastic carcinoma, Ameloblastoma

Table 2 (continued)

Marker	Function	Diagnostic marker
P63, epithelial membrane antigen (EMA), Filaggrin	P63: transcription factor for teeth and mammary glands development EMA: transmembrane muci expressed on epithelial cells Filaggrin: filament-associated protein that binds to keratin fibers	clear cell odontogenic carcinoma

genome, transcriptome or proteome of saved samples with sufficient integrity and quality [30]. As another strategy, organotypic cultures were suggested in an experimental model for detection of molecular aspects of odontogenic tumors. The organotypic cultures provide ex vivo imitated neoplastic microenvironment with suitable reproduction of the growth pattern. In addition, organoid represents in vitro tumor model-study for metastasis and invasion, drug screening, immunotherapy, clinical trial, hallmarks association with prognosis and evolution of personalized anti-cancer therapy [31]. Organoid provide optional treatment for patient′ s tumor attention to site, stage and personal factors and variation in their genetic profile as personalized medicine. For example, different drug dosage or combination therapy can be applied in an organoid and the outcome determined the best choice for therapy [32].

Further, organoid led to collect biobank from different tumor cell lines and study genome features following cell propagation and development, so alternation in genetic profile such as mutations can be studied between tumouroid line and a derived tumor [33]. Also, we propose application of biobank with collection of odontogenic lesion types from different geographical regions can help us to define a distinct profile change in the genome for therapy.

The first study with long-term 3D primary culture was performed for odontogenic myxoma and the cemento-ossifying fibroma with cell expansion more than one month [34]. More investigation is continued for human head and neck tumors with organoid. For example, 3D organoid provides target therapeutic screening based on a non-surgical method to evaluate ameloblastoma pathogenesis and progression for BRAF and LGR5 inhibition [35]. More knowledge about biology and molecular behavior of odontogenic tumors increases our information for better understanding of their nature. Also, we think more investigation and studies are needed to gain these knowledges that can shift therapeutic approaches to target therapy. Detection of genetic factors that are involved in molecular pathogenesis of odontogenic tumors helps us in target therapy, special gene therapy when surgical treatments are contraindicated [36]. In this manner we can find ways for other odontogenic lesions as non-surgical therapeutic approaches (Fig. 2).

Conclusion

The restricted origin of odontogenic tumors (epithelial, mesenchymal or mixed) might appear with similar morphology and histochemical features in differential diagnosis. So, mistaken in diagnosis provides improper treatment because some odontogenic tumors need invasive therapy but others not. The molecular advanced technology like next-generation sequencing or “omics” can identify all aspects of tumor changes and help us to consider more candidates in diagnosis, prognosis and therapeutic approaches. Target therapy in oral pathology needs more investigation, and it seems ethiopathological information of familial odontogenic tumors in different geographical regions can help us to modify our attitude to pathogenesis of these lesions.

Table 3 Alternation of genetic profile in odontogenic tumors

Odontogenic tumor type	Alternation in gene expression	Current gene mutation	Rare gene mutation
Ameloblastic carcinoma	Overexpression of *SOX2* and *PITX2* (TF in Wnt pathway) High level of ki-67 protein Increased *POLR2J*, *CDKN2C* and decreased *EIF3S5* expression	63% of cases *BRAF* (*V600E*), 16–39% *smoothened* (*SMO*)	*FGFR2, RAS (KRAS, NRAS, HRAS), PIK3CA, CTNNB1, SMARCB1*
Primary intraosseous carcinoma, NOS	- Increased NF-6, epidermal keratin type II, MEF2C transcription factor, metalloproteinase, tyrosine phosphatase CIP2, TGFB BP, mitogen inducible gene-2 and oncofetal antigen 5T4 expression - Decreased epidermal keratin types 1,13,15,16, TGFB3R, differentiation dependent A4 protein, ribosomal protein L3, L8, L28, L29, L31, L35, S3, S5, S10, S24, ZFP, DNA BP FKHL15, PRAD1 and ARF-activated phosphatidylcholine specific phospholipase D1a expression		
Sclerosing odontogenic carcinoma			
Clear cell odontogenic carcinoma	Increased *ADAM28*, *FGF9*, *S100A7*, *PTCH1*, *MMP1,2,12*	≥ 80% show *EWSR1* rearrangement	*ATF1* as translocation partner, BRAF (V600E)
Ghost cell odontogenic carcinoma	Overexpression of p53		*UBR5*, *APC* (related to Gardner syndrome: familial colorectal polyposis)
Ameloblastoma	Overexpression of *SMO*, *BRAF* Increasing *ODAM*, *FOS* and decreasing *CTBP2*, *STK19* expression	≥ 90% demonstrated MAPK pathway mutation (most *BRAF V600E*), others: *RAS* (*KRAS*, *NRAS*, *HRAS*), *FGFR2* Non-MAPK pathway: *SMO*, *SMARCB1*, *CTNNB1*, *PI3CA*	
Ameloblastoma, unicystic type (UAM)		*BRAF* (*V600E*)	
Ameloblastoma, extraosseous/peripheral type		β-catenin mutation in Wnt pathway	
Metastasizing ameloblastoma			
Squamous odontogenic tumor		*NOTCH* receptor and ligands, ameloblastin (*AMBN*), *metallotheionein*	
Classify epithelial odontogenic tumor (CEOT)	Over expression of *AODAM* Loss of *p53* expression	*PTCH, p63, EGFR, bcl-2*	*SHH, Gli1, Gli2*
Adenomatiod odontogenic tumor			
Benign mixed epithelial and mesenchymal odontogenic tumors			
Ameloblastic fibroma (AF)		*BRAF* (*V600E*) Lost genetic loci in *p53* (17p13) and *CHRNB1* (17p13)	
Primordial odontogenic tumor	Increasing *DMP1*, decreasing *IBSP* and *BGLAP* expression		
Odontoma Odontoma, compound type Odontoma, complex type			Manifect in Gardner syndrome: familial colorectal polyposis
Dentinogenic ghost cell tumor			
Benign mesenchymal odontogenic tumors			
Odontogenic fibroma			
Odontogenic myxoma/myxofibroma	Downregulation of *PRKAR1A*		

Table 3 (continued)

Odontogenic tumor type	Alternation in gene expression	Current gene mutation	Rare gene mutation
Cementoblastoma			
Cemento-ossifying fibroma	Increasing *CTNNB1*, *TCF7*, *NKD1*, *WNT5A*, *HMMR* and decreasing *CTNNBIP1*, *FRZB*, *FZD6*, *RHOU*, *SFRP4*, *WNT10A*, *WNT4* expression	mutation in *CDC73* (*HRPT2*) gene	

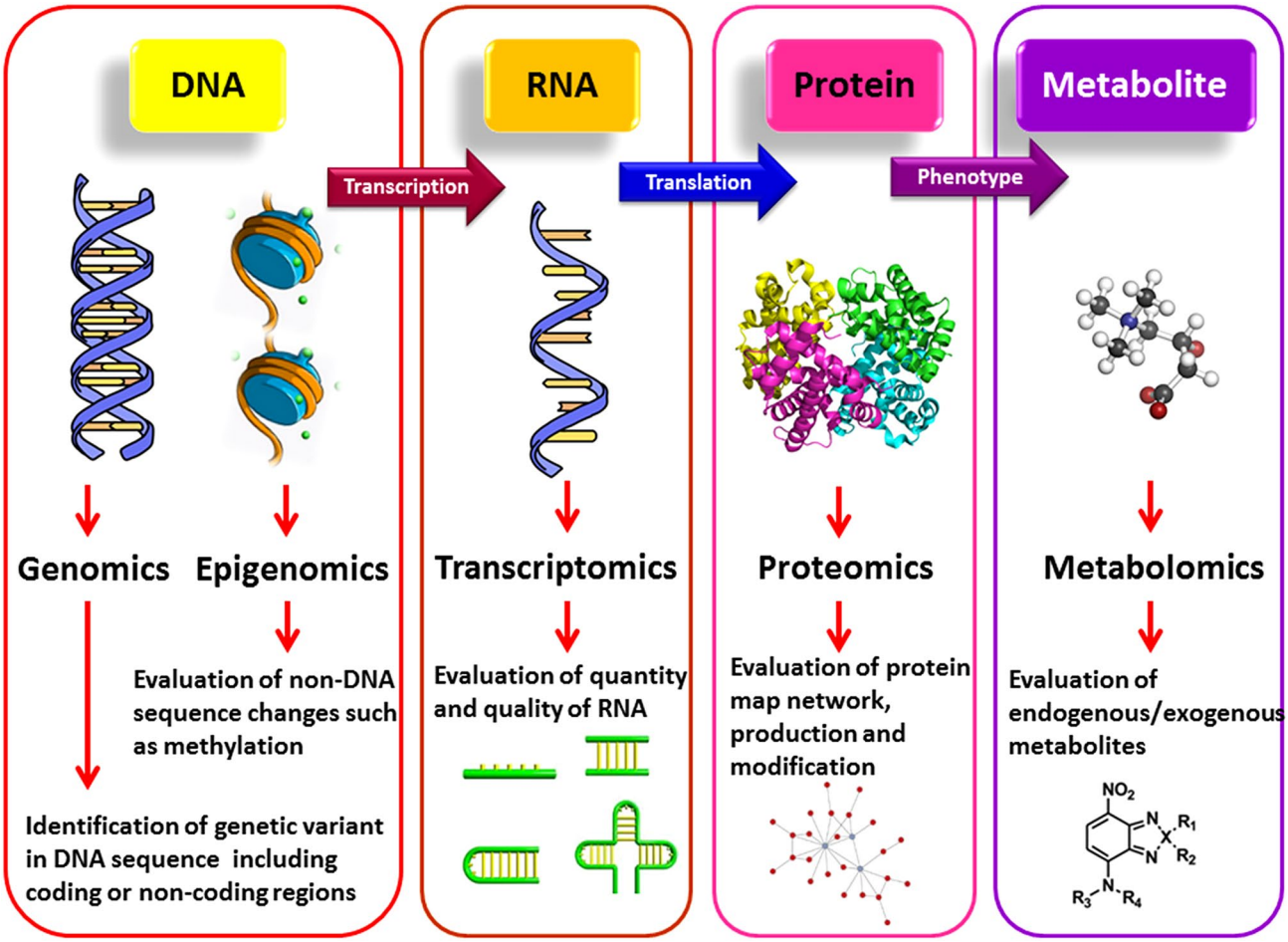

Fig. 1 Different main levels of "-omics" technology for evaluation of comprehensive molecules in cell including genetic variants in DNA sequence (Genomics), non-DNA sequence alternation such as histone modification and methylation (Epigenomics), analysis of expression and structural changes in RNA and variants like splice sites (Transcriptomics), evaluation of expression, modification and net protein interactions (Proteomics) and description of functional metabolites in cell (Metabolomics). The mix of different type of "-omics" technology can help us in diagnose, prognoses and therapeutic approaches of tumors

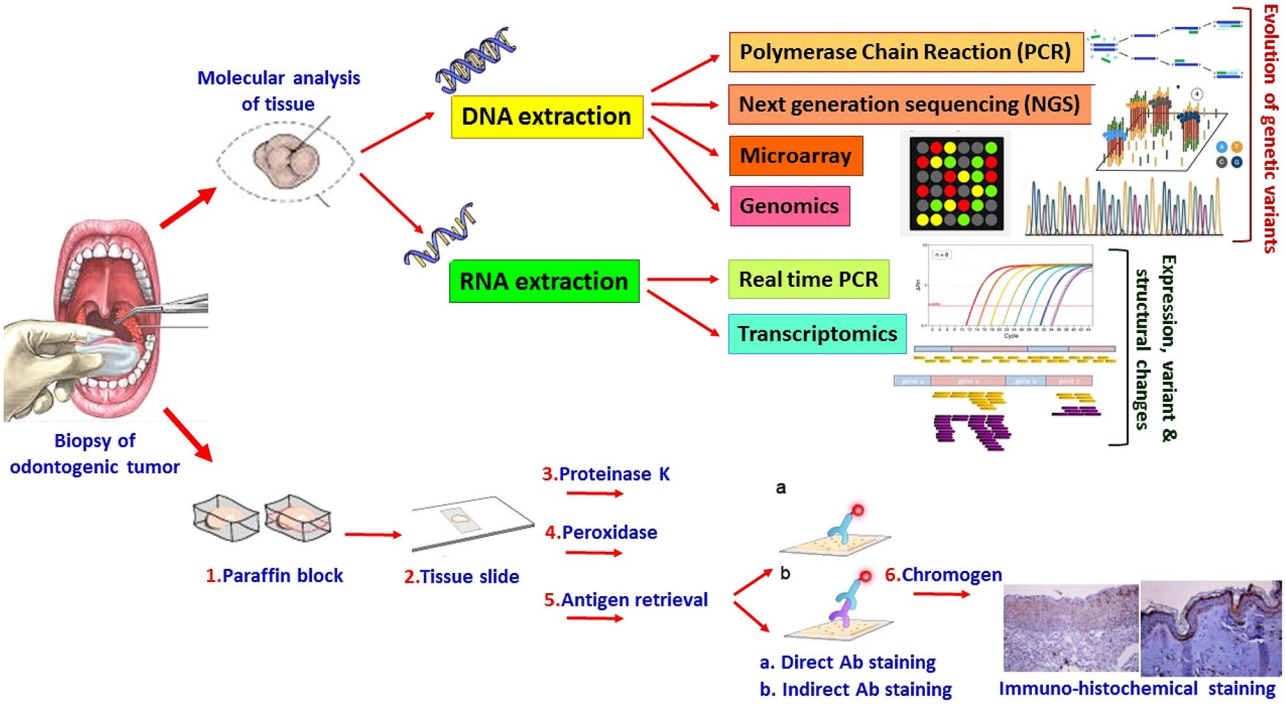

Fig. 2 Summary of molecular genetics approaches and immune-histochemical method in diagnosis of odontogenic tumors

Declarations

Conflicts of interest The authors declare that there are no conflicts of interest.

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