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REVIEW ARTICLE

Oral Cytokeratins in Health and Disease

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ABSTRACT

The dynamics of oral mucosa is known by its inherent defensive nature. Certain areas demand tough shield when subjected to mechanical insults. This is met by structural scaffolding material referred as cytoskeleton comprised of intracellular protein filaments called cytokeratins in the surface squames of oral epithelia. They also equally contribute towards the architecture of odontogenic apparatus and salivary gland. Differentiation of epithelial cells within stratified epithelia regulates the expression of specific keratin gene. Any mutation in, or autoantibodies to keratins, desmosomal and cornified envelope proteins is translated into genetic and acquired human disorders. Sound knowledge of structural proteins, their expression, distribution and function plays a vital role in acquainting with these disorders and their application as differentiation markers. Thus, they form an integral aid in diagnostic pathology and may be instrumental in the future interventions by gene therapy. This review focuses on basics to current updates on oral cytokeratins with an emphasis on the genetic and acquired disorders of cytokeratins with oral implications.

Keywords: Cytokeratins, Cytokeratin markers, Keratin genes, Keratin disorders.

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INTRODUCTION

Oral epithelium has regional diversity corresponding to functional needs as it is subjected to different forms and intensity of stress which demand tougher epithelial cells. Thus, this need is met by the formation of intracytoplasmic filamentous arrays called keratins. 'The keratins' are most diverse and an outstanding group of proteins belonging to the intermediate filament (IF) family which constitute about 80% of the total protein content in differentiated cells of stratified epithelia.[1-3]

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The word keratin comes from the Greek word '*kera*' meaning horn.[4] Keratins are defined as intermediate filament forming proteins, (10 nm in diameter) with specific physicochemical properties, produced in any vertebrate epithelia.[5] They form the cytoskeletal structural proteins of stratified keratinizing epithelia.[6]

HISTORY

A century ago in 1850, the word 'keratin' first appeared in literature to denote a material that constituted the hard tissues like animal horns and hooves.[4] William T Astbury and Francis Crick contributed to the structure of keratin, following which Sun and Green popularized the monoclonal keratin antibodies. The identification of types I and II subunits in keratin and requirement of both these types to constitute a stable keratin assembly was noted by Fuchs and co-workers. All these developments were followed by extensive research in biology and pathology using monoclonal antibodies with the discovery of Epidermolysis bullosa simplex (EBS) as the first disease of IF.[7]

KERATINIZATION IN ORAL EPITHELIA

Oral epithelia demonstrate one of the 2 patterns of epithelial maturation (Fig. 1).[2]

1. Keratinization—mucosa matures by formation of surface layer of keratin.
   a. Orthokeratinization—refers to the absence of nuclei in the surface layer of squames on maturation.
   b. Parakeratinization—refers to the retention of pyknotic nuclei in the surface layer of squames on maturation.[2]
2. Nonkeratinization—refers to maturation with absence of keratin layer. Hence the surface cells retain their nuclei with sparse keratin filaments in the cytoplasm.[8]

Meeting the functional demands, gingiva demonstrates both types of epithelia-keratinized (e.g. Attached and free gingiva) and nonkeratinized (e.g. Sulcular and junctional epithelia).[2]

The following terms denote pathologic states:

- Keratosis: When keratinization occurs in a normally nonkeratinized tissue, it is referred to as keratosis.
- Parakeratosis: When normally keratinizing tissue, such as epidermis, becomes parakeratinized, it is referred to as parakeratosis.[9]

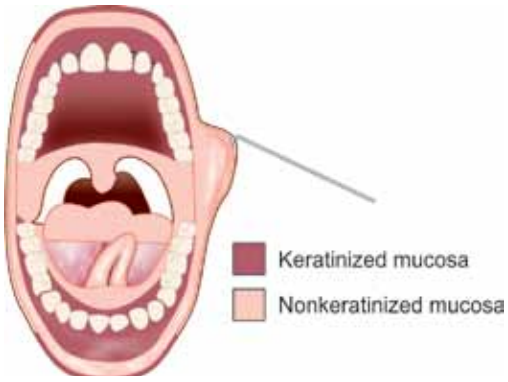


Fig. 1: Keratinization in oral mucosa

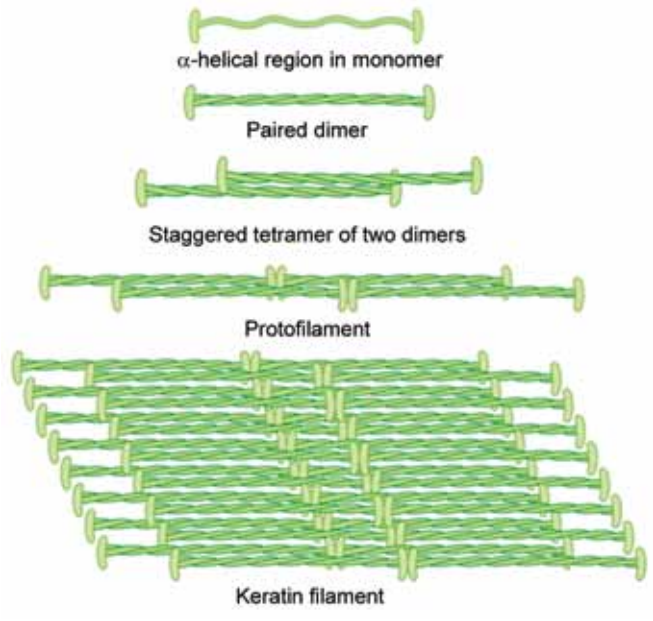


Fig. 2: Assembly of keratin filament

FACTORS INFLUENCING EPITHELIAL DIFFERENTIATION

Debbie Tudor et al in 2004 reviewed all the experimental evidence on the 'Intrinsic Patterns of Behavior of Epithelial Stem Cells' and concluded that the intrinsic property of epithelial stem cells and mesenchymal modulation of stem cells determine the epithelial phenotype. In addition, mesenchymal modulation of the basic stem and amplification pattern is essential to produce and maintain most epithelial structures.[10]

Retinoids and calcium also influence the normal terminal differentiation of epithelium. Vitamin A and its analogs, retinoids affect the gene expression by a group of nuclear receptor proteins.[11] Deficiency of vitamin A leads to squamous metaplasia and epithelial keratinization whereas, excess vitamin A inhibits keratinization.[12] Also, high calcium concentrations are necessary for stratification and desmosome assembly.[11]

KERATIN STRUCTURE

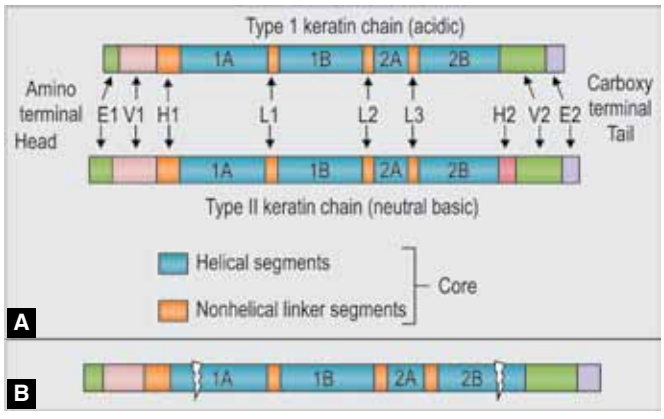
Keratins are obligate heterodimer proteins, expressed in pairs of types I and II proteins.[13] The molecular weight of human keratins ranges from 44 to 66 kDa.[1]

Filament assembly begins by parallel association of a type I chain with its type II counterpart to form a paired dimer. Two such paired dimers associate in an antiparallel fashion to form a staggered tetramer. Two tetramers pack together laterally to form the protofilament. Eight such protofilaments are twisted into a rope which forms the keratin filament. Each individual keratin filament therefore has a cross section of 32 individual α helical coils. Strong lateral hydrophobic interactions stabilize the polypeptide chains. Keratin filaments are subsequently bundled and assembled into macromolecular networks that radiate throughout the cytoplasm (Fig. 2).[14,15]

BASIC MOLECULAR STRUCTURE OF KERATIN POLYPEPTIDE CHAINS

All keratin molecules contain a central rod domain of 310 aminoacids with α-helical conformation. This central core is made up of four subdomains (1A, 1B, 2A, 2B) separated by three nonhelical linker sequences (L1, L2 and L3) (Fig. 3A). Diversity among keratin filaments resides in nonhelical extensions at the amino and carboxy terminals (H, V and E end domains)[15-18]Further, there are two highly conserved helix boundary sequence motives on each rod, called helix initiation peptide (HIP) in the 1A domain and the helix termination peptide (HTP) at the end of helix 2B. Any mutations in these regions, lead to more severe disease phenotypes than the other regions (Fig. 3B).[19]

Glycine is the most abundant residue in cytokeratins. The heads and/or tails of epidermal keratins are glycine and phenylalanine rich but alanine poor and those of simple-type epithelial keratins are enriched in acidic and/or basic residues.[20]



Figs 3A and B: (A) Molecular structure of type I and II keratin, (B) Regions of 'hot spot' mutations in keratin ()

Table 1: KFAPs expressed in oral epithelia

Class of KFAP	*Example*	*Description*	*Significance*
Class I	Filaggrin	• Low molecular weight, cationic protein that binds the keratin in tight arrays. • Synthesized in the granular layer and stored in keratohyalin granules. • Converted to filaggrin upon transition of granular cells tocornified cells. • Functions: Aggregates and aids keratin filaments in dense packing within the cornified layer.	Marker to distinguish nonkeratinized epithelia from keratinized epithelia.
Class II	Trichohyalin	• High molecular weight and binds keratin in loose network arrays. • Expressed in keratinizing papillae of the tongue, nail matrix, new born fore skin epidermis. • Functions: Intercellular cementing, cross bridging the proteins, regulation of calcium dependent enzymes	
Class III	Loricrin	• Expressed in the superficial layers of keratinized and nonkeratinized oral epithelia • Function: Binds to the ends of keratin and contributes towards cornification	Markers to determine the extent of cell differentiation.
	Desmosomal proteins	• They include integral proteins (desmoglein and desmocollin), cytoplasmic adapter proteins (desmoplakin and plakoglobin) and plaque associated proteins (plakophilin, envoplakin and periplakin). • Function: Bind epithelial cells and help in attachment of keratin intermediate filament to cell surface.	Antibodies to desmosomal proteins are demonstrable in autoimmune diseases like pemphigus.

KERATIN FILAMENT ASSOCIATED PROTEINS (KFAPS)

KFAPs are nonfilamentous, structural proteins that interact with keratin filaments. They are produced in the keratinocytes of the stratum granulosum and stored in keratohyalin granules. KFAPs are needed for the function of the intermediate filament network and for the shape, stability, and motility of epithelial cells.[11]

There are three classes of KFAPs. A brief description and clinical relevance of KFAPs expressed in oral epithelia are collated in Table 1.[6,11,21-23]

Involucrin, Transglutaminase

Involucrin is yet another KFAP, by enzymatic cross-linking via a particulate transglutaminase is involved in the formation of cornified cell envelope (CCE). They are present in buccal and palatal epithelia and are useful markers of cell differentiation.[6]

KERATIN GENES

In 2006, Schweizer et al developed a new consensus nomenclature for hard and soft keratins, which includes the highest number of members in humans with 54 distinct functional genes: 28 type I keratin genes (17 epithelial keratins and 11 hair keratins) and 26 type II keratin genes (20 epithelial keratins and 6 hair keratins). The keratin genes are located at two different chromosomal sites: chromosome 17q21.2 (type I keratins, except K18) and chromosome 12q13.13 (type II keratins including K18) in humans. The keratin genes are designated as KRT1, KRT2, KRT3, etc.[24]

CLASSIFICATION OF KERATINS

A working classification of keratins based on various criteria is proposed in the Flow Chart 1.[1,21]

FUNCTIONS OF KERATINS

Keratins primarily serve as the backbone of vertebrate epithelial cells. In addition, keratins serve diverse functions as represented in the Flow Chart 2.[19,25]

DEMONSTRATION OF KERATINS

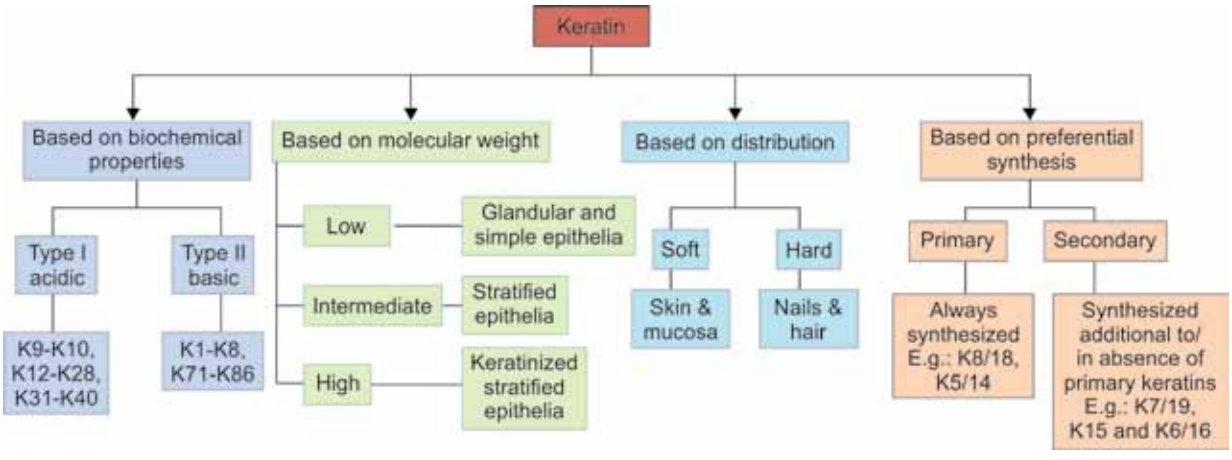
Various routine, special and fluorescent stains may be used to demonstrate cytokeratins in histological sections (Table 2).[26,27]

Other staining methods include Dane–Herman method, Schiff reagent after oxidation with performic acid, aldehyde fuchsin, levafix red violet.[27,28]Immunohistochemical staining is the golden tool for cytokeratin demonstration which is discussed later in this article.

Table 2: Various histological stains for demonstration of keratin

Stain	*Result*
Hematoxylin and eosin stain	Pink
Ayoub-Shklar stain	Brilliant orange
Phloxine-tartrazine method	Red
Modified PAP stain	Magenta pink
Gram stain	Blue
Aldehyde fuchsin technique	Purple
Congo red method	Orange-red
Performic acid- Methylene blue/ alcian blue technique	Blue
Thioflavin T fluorescent technique	Yellow fluorescence
Auramine- Rhodamine fluorescent method	Yellow fluorescence

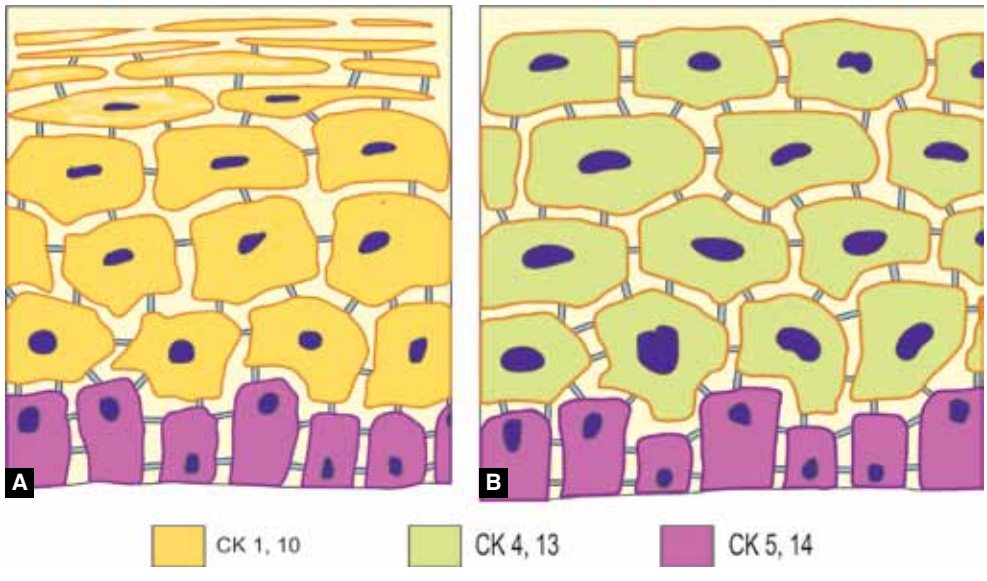
Flow Chart 1: Classification of keratin



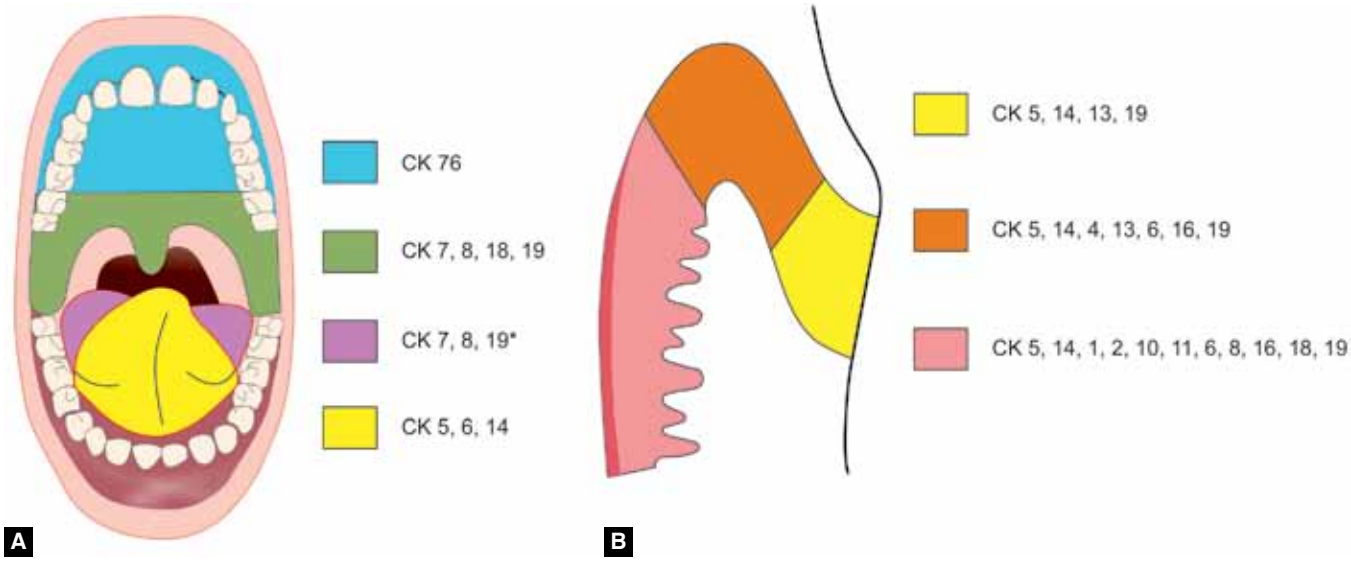
CYTOKERATINS

Mammalian keratins are subdivided into two distinct groups based on their structure, function and regulation. Cysteine-rich keratins are tougher in nature and constitute the 'hard' keratins found in epidermal appendages (hair and nails), whereas loosely packed bundles of cytoplasmic keratin filaments in epithelial cells are termed as 'soft or cyto' keratins.[29-31]

Cytokeratins are the basic structural proteins of epithelial cells. They are abundant in oral cavity, salivary gland epithelia and are expressed during odontogenesis. Also, cytokeratins are the leading biomarkers in diagnostic pathology.

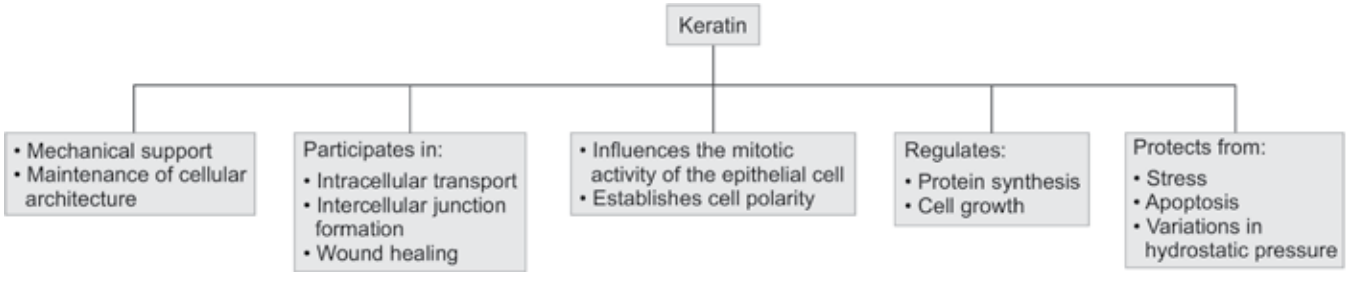


Figs 4A and B: Normal cytokeratin distribution in oral mucosa: (A) Keratinized epithelia, (B) non-keratinized epithelia



Figs 5A and B: (A) Regional variation in keratin distribution in normal oral mucosa, (B) cytokeratin distribution patterns in normal gingiva. *Expressed by taste buds

Flow Chart 2: Functions of keratin



CYTOKERATIN DISTRIBUTION

Cytokeratin distribution is highly specific and varies with site, type of epithelium and extent of differentiation.[1] Hence keratin expression is a sensitive and specific marker for assessment of differentiation in epithelial cells.

Cytokeratin Distribution in Normal Oral Epithelia

Cytokeratin distribution in normal oral epithelia is represented in Figures 4A and B.[9,11,15]

Further, the regional specificity of keratin expression may be attributed to intrinsic specialization of regional keratinocyte stem cells.[32] Figures 5A and B depict the regional variation in cytokeratin distribution in oral mucosa and gingiva.[1,2,9,15]

Also, CK7, 8, 18, 19 are the markers for simple epithelia and merkel cells. Hyperproliferative epithelia are known to express CK6, 16.[11,15]

Cytokeratin Distribution in Salivary Epithelia and Odontogenic Tissues

Cytokeratin distribution in salivary epithelia and odontogenic tissues is briefed in Table 3.[2,33-36] The typical intermediate filament of odontogenic epithelium is CK14, observed in the dental lamina, the reduced enamel epithelium and in almost all cells of the enamel organ except for preameloblasts and secreting ameloblasts.[33]

DISORDERS OF KERATIN

The field of cytokeratins has scope for exhaustive research and this is due to increasing number of new diseases being explored. Disorders in keratin may be genetic or acquired. Since the discovery of the first genetic disorder of keratin epidermolysis bullosa simplex (EBS), numerous keratin mutations are being identified as cause of several skin and mucosal disorders. Also, abnormal keratinization is part of several acquired oral diseases. A working classification of oral keratin disorders is depicted in Flow Chart 3.

GENETIC DISORDERS OF KERATIN

A wide array of keratin disorders is attributable to mutations in various genes and majority are result of point mutations.[6] They may exhibit abnormality in both cyto (soft) and hard keratins. Also, the defective genes may be located within (e.g.: Epidermolysis bullosa simplex, Pachyonychia congenita) or outside the α-helical rod domain (Nonepidermolytic palmoplantar keratoderma). In addition,

Table 3: Cytokeratin distribution in salivary epithelia and odontogenic tissues

Cytokeratins	*Distribution*
Salivary epithelia	
CK 14	Myoepithelial cells and basal cells (ductal nonluminal cells)
CK 18, 19	Epithelium elements of salivary gland
CK 7, 8, 18, 19	Luminal duct cells
CK 8, 18	Epithelium of striated and intercalated ducts
Odontogenic tissues	
CK 7, 13, 14, 19	Enamel organ
CK 14	Most cells of enamel organ (Odontogenic epithelial marker)
CK 7	Stellate reticulum and HERS
CK 19	Preameloblasts and secretory ameloblasts (secretory differentiation)
CK 5/19	Cell rests of Malassez

several diseases are attributable to abnormalities in KFAP (Pemphigus, Darier's disease, Dyskeratosis congenita).[20] Common genetic disorders of keratin with oral involvement are briefed in Table 4.[37-45]

ACQUIRED KERATIN DISORDERS

Several oral disease processes demonstrate significant non-genetic abnormalities in keratinization. The most common are briefed in the Table 5.[46-48]

A thorough description of keratin from basics to disorders with oral implications is dealt with. The following part discusses the oral cytokeratins in specific, their expression patterns in normal and disease process. Also, highlighted is the diagnostic role of cytokeratins in the present era.

SIGNIFICANCE OF CYTOKERATINS IN DIAGNOSTIC ORAL PATHOLOGY

Cytokeratins demonstrate specific expression pattern which is site- specific and varies with the level of differentiation. This property of cytokeratin has evolved as a potential epithelial differentiation marker in cell biology, embryology and surgical pathology. Cytokeratins are the 'gold standard markers' in immunohistochemical diagnosis, classification and subtyping of carcinomas and detection of unclear metastasis. Soluble cytokeratin protein fragments detection is recently adopted as a tool to check tumor load and prognosis of carcinomas.[49,50] A key characteristic of keratins that makes them useful in pathology is the relative stability of expression even after transformation to pathological states.[7] Hence, selected cytokeratins along with other specific markers are the definitive diagnostic tools in current clinical pathology.[1]

Recently, it is been stated that cytokeratin expression is not restricted to carcinomas, few sarcomas with true epithelial differentiation (e.g.: synovial and epithelioid sarcomas) also are positive for specific cytokeratin types.[51] Cytokeratins 7 and 19 are expressed by synovial sarcomas and cytokeratins 5/6 are specific for epithelioid sarcomas.[52-54] Also, few specific nonepithelial tumors (smooth muscle tumors, melanomas and

Flow Chart 3: Working classification of oral keratin disorders

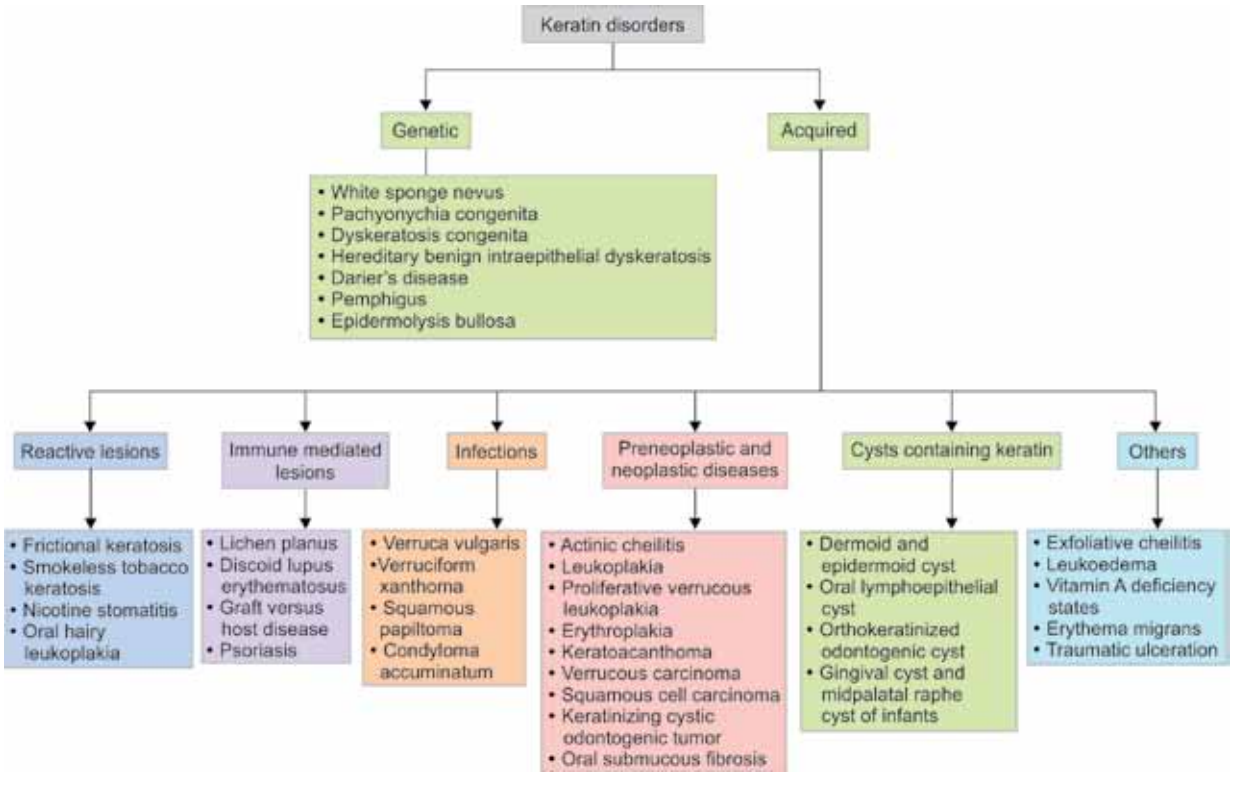


Table 4: Genetic disorders of keratin with significant oral manifestations

Disease	*Defect*	*Clinical features*		*Oral manifestations*	*Histopathologic features*
		Site	*Appearance*		
Epidermolysis bullosa simplex	K5 and 14 autosomal dominant inheritance	Hands and feet	Blisters that heal without scarring	Mucosal involvement uncommon; mild involvement- gingival erythema, tenderness, recession and reduction in depth of buccal vestibule	Intraepithelial clefting
White sponge nevus	K4/13 Autosomal dominant inheritance	—		Asymptomatic, symmetrical, thickened white, corrugated or velvety, diffuse plaques affect buccal mucosa bilaterally	• Epithelial hyperplasia and hyperparakeratosis • Perinuclear condensation of keratin tonofilaments in the superficial layers of epithelium
Pachyonychia congenita	K6A, K6B, K6C, K16 or K17 Autosomal dominant inheritance	Nails	Free margins get lifted due to accumulation of keratinaceous material in nail beds	Hyperkeratosis of oral mucosa	Hyperparakeratosis and acanthosis with perinuclear clearing of the epithelial cells
		Palmar and plantar surfaces	Hyperkeratosis		
Dyskeratosis congenita	DKC1 gene Predominantly X-linked recessive inheritance	Skin	Abnormal pigmentation	Leukoplakic lesions on tongue, buccal mucosa- one third become malignant	Hyperorthokeratosis with epithelial atrophy complication: Progression to squamous cell carcinoma
		Nail	Dystrophy		
		Mucosa	Leukoplakia		
Hereditary benign intraepithelial dyskeratosis	HBID gene on chromosome 4 Autosomal dominant inheritance	Eye	Elevated epibulbar plaques and hyperemic conjunctival blood vessels	Thick, corrugated white plaques on buccal and labial mucosa	Hyperparakeratosis acanthosis and dyskeratosis (cell-within–a-cell phenomenon)
Darier's disease	ATP2A2 gene Autosomal dominant inheritance	Skin of trunk and scalp	Numerous erythematosus, pruritic papules	Asymptomatic multiple, white, flat-topped papules on hard palate and alveolar mucosa- may fuse to give a cobblestone mucosal appearance	Dyskeratosis in the form of corps and grains, acantholysis, elongated rete ridges
Pemphigus	Desmoglein 1and 3 (HLA gene)	Skin	Flaccid vesicles and bullae that rupture to leave an erythematosus, denuded surface	Superficial ragged erosions and ulcerations anywhere in oral cavity	Acantholysis, intraepithelial clefting and basal layer of cells resemble 'row of tombstones'

endothelial cell tumors) may demonstrate anomalous cytokeratin expression in 'dot-like' pattern. Thus in any scenario, cytokeratins provide major clue to diagnosis.[51]

Cytokeratin Expression in Oral Epithelial Pathology

CK8 and CK18 are described as surrogate markers of malignant transformation in a squamous epithelium. In a study by Kanwar Deep Singh Nanda et al (2012), CK8 and CK 18 expression were absent in normal buccal mucosa, while intense expression was noted in dysplasia, OSF, and OSCC. This could be due to de novo expression of CK8 and CK18 in previously negative epithelium, which during malignant transformation might be regarded as a return to an embryonal expression pattern.[55]

Table 5: Acquired oral disorders of keratin

Acquired keratin disorder	*Oral manifestations*	*Keratin pathology*
Reactive lesions		
Frictional keratosis	Rough, white keratotic lesion in areas of mechanical irritation	Hyperkeratosis
Smokeless tobacco keratosis	White plaque/distinct pouch on the mucosa in direct contact with smokeless tobacco	Hyperkeratosis, parakeratin chevrons
Nicotine stomatitis	Diffusely grey/white palatal mucosa with numerous slightly elevated papules with punctuate red centers	Hyperkeratinization
Oral hairy leukoplakia	Appearance ranges from faint white vertical streaks to thickened and furrowed areas of leukoplakia often on lateral border of tongue	Hyperparakeratosis with surface corrugations
Immune mediated lesions		
Lichen planus	Asymptomatic, interlacing white lines on buccal mucosa bilaterally is common (Whickham's striae)	Hyperkeratosis
Discoid lupus erythematosus	Oral ulcers on buccal mucosa, gingiva and vermillion border	Hyperkeratosis
Infections		
Verruca vulgaris	Painless papule/nodule with papillary projections on vermilli on border, labial mucosa or anterior tongue	Hyperkeratosis
Verruciform xanthoma	Painless, slightly elevated sessile nodule with papillary surface on gingiva and alveolar mucosa	Hyperparakeratosis with parakeratin plugging
Preneoplastic and neoplastic diseases		
Actinic cheilitis	Lip appears atrophic, finely wrinkled and swollen with mottled areas of hyperpigmentation and with keratosis	Hyperkeratosis
Leukoplakia	Nonscrapable white patch on lip vermillion, buccal mucosa and gingiva	Hyperkeratosis
Erythroplakia	Well demarcated erythematous macule or plaque with a soft, velvety texture on floor of the mouth, tongue and soft palate	Lack of keratinization
Keratoacanthoma	Firm, nontender sessile nodule on vermillion border of lips	• Dyskeratosis- individual cell keratinization and keratin pearls • Hyperkeratosis of surface epithelium with keratin plugging
Verrucous carcinoma	Diffuse, white, painless thick plaque with verruciform surface projections often corresponding to the site of chronic tobacco placement	Hyperkeratosis with parakeratin plugging
Squamous cell carcinoma	Nonhealing ulcer or exophytic growth	Dyskeratosis- individual cell keratinization and keratin pearls
Keratinizing cystic odontogenic tumor	Asymptomatic/painful swelling in the posterior body and ascending ramus region	Hyperparakeratosis, corrugated surface keratin
Others		
Exfoliative cheilitis	Persistent scaling and flaking of vermillion border of the lips	Excessive production and subsequent desquamation of keratin

Cytokeratin Expression in Salivary Neoplasms

The CK profiling in salivary gland pathology has limited applications. Although non specific, the CKs help in delineating dual luminal-abluminal differentiation.[56] A study by Nikolaos G Nikitakis et al (2004) revealed that MEC often express CK 7 in contrast to squamous cell carcinoma and salivary duct carcinoma showing a higher frequency of CK7/CK20 immunophenotype compared to the rest of malignant salivary gland tumors.[57]Another study by Randall et al (2013) showed that CK 5/6 was specific for MEC and thus may be used as an adjunct in discriminating MEC from highly aggressive salivary duct carcinoma.[58]

Cytokeratin Expression in Odontogenic Cysts

Cytokeratin expression in odontogenic cysts namely odontogenic keratocyst (OKC), dentigerous cyst (DC) and radicular cysts have been extensively studied but no consistent differences have been noted.[59] An interesting study by Smith and Matthews in 1991 revealed a strong expression of CK 1/10/11 by OKC, while DC and radicular cyst were negative. Also, a strong reaction of OKC lining for CK16 suggested its high proliferative activity.[60] Yet other studies have also shown cytokeratin 16 expression in dentigerous and radicular cysts.[59] Stoll et al in 2005 concluded that CK17 and 19 are valuable in distinguishing

Table 6: Cytokeratin expression in odontogenic tumors

Cytokeratin	*Expression*
CK 14	Adenomatoid Odontogenic tumor (AOT)
CK 13, 14, 19	Ameloblastoma
CK 14, CK 7*, CK 13*, CK 19*	Calcifying epithelial odontogenic tumor (CEOT)
CK 13, CK14, CK 7*	Ameloblastic fibroma
CK 7, 14	Odontoma

*Expressed occasionally

OKCs from other odontogenic cysts (OKC with 93% expression of CK17 and CK19 expression in contrast to DC and radicular cysts which showed 35% CK 17 positivity and 43% CK 19 positivity).[61]

Cytokeratin Expression in Odontogenic Tumors

Studies have revealed specific keratin expression in different odontogenic tumors (Table 6).[33]

CONCLUSION

An insatiable curiosity and appetite to explore the amazing world of oral cytokeratins widens the horizon in diagnostic pathology. Moreover, the field of cytokeratins is exhaustive and dynamic, but equally interesting. New cytokeratins and corresponding genes, their role as etiological factors, diagnostic markers as well as prognosticators are constantly being updated. Hence updating oneself with the new concepts is paramount.

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