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Review Article

KERATIN THE OUTSTANDING PROTEIN IN ORAL CAVITY: A NARRATIVE REVIEW

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ABSTRACT

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. 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. Keartins are classified into 20 major groups starting from K1 to K20. In epidermal cells, keratin intermediate filaments connect with desmosomes to form extensive cadherin - mediated cytoskeletal architectures. Koulis et al explored the biochemical nature of the connections between keratin filaments and desmosomes in epidermal keratinocytes. Biosynthesis occurs in 2 phases – In an initial phase, keratin production keeps pace with the increasing rate of total protein synthesis. In second phase, keratin production outpaces total protein synthesis and / or nonkeratin proteins are selectively degraded. Keratin expression in normal tissue works for the following keratinisation, also functions in glandular tissue.

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.

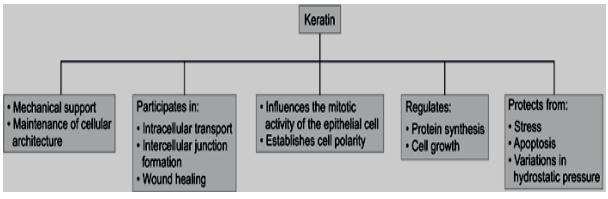
Oral epithelia demonstrate one of the 2 patterns of epithelial maturation

Keratinization-mucosa matures by formation of surface layer of keratin.

- Orthokeratinization-refers to the absence of nuclei in the surface layer of squames on maturation.
- Parakeratinization-refers to the retention of pyknotic nuclei in the surface layer of squames on maturation.

Nonkeratinization-refers to maturation with absence of keratin layer. Hence the surface cells retain their nuclei with sparse keratin filaments in the cytoplasm.

- Meeting the functional demands, gingiva demonstrates both types of epithelia-keratinized (e.g. Attached and free gingiva) and nonkeratinized (e.g. Sulcular and junctional Epithelial.)
- Cytokeratins are proteins of keratin containing intermediate filaments found in the intracytoplasmic cytoskeleton of epithelial tissue.The term "cytokeratin" began to be used in the late 1970s, when the protein subunits of keratin intermediate filaments inside cells were first being identified and characterized.In 2006 a new systematic nomenclature for keratins was created and now the proteins previously called "cytokeratins" are simply called keratins.



All mammalian cells contain a complex intracytoplasmic cytoskeleton composed of principal structural units and associated proteins: intermediate filaments with a diameter of

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7-11nm, actin-containing microfilaments with a diameter of 5nm and tubulin containing microtubules with a diameter of 25nm. Cytokeratins (CKs), the major structural proteins of epithelial cells, display the greatest heterogeneity of all intermediate filament proteins. They form a complex family of at least 30 polypeptides, divided almost equally between two gene families - type I and type II keratins. They are distinguishable from one another on the basis of isoelectric point and molecular weight.

Classification

The first attempt at providing comprehensive keratin nomenclature dates back to 1982. Moll et al (1982) used 2-D isoelectric focussing and SDS-PAGE to map the keratin profiles of large number of normal human epithelia, tumours and cultured cells. They grouped into two types- basic to neutral type II keratins as K1-K8 and acidic type I keratins as K9-K19.

Molecular characteristics of keratins[1]

Keratin Names by Moll	Chromosomal localization	Mol.wt ($x10^3$)	Type of IF	PI
K1	12	67	II	7.8
K2	12	65	II	6.1
K3	12	64	II	7.5
K4	12	59	II	7.3
K5	12	58	II	7.4
K6	12	56	II	7.8
K7	12	54	II	6.0
K8	12	52	II	6.1
K9	17	64	II	5.4
K10	17	56.5	I	5.3
K11	17	56	I	5.3
K12	17	55	I	4.9
K13	17	51	I	5.1
K14	17	50	I	5.3
K15	17	50	I	4.9
K16	17	48	I	5.1
K17	17	46	I	5.1
K18	17	45	I	5.7
K19	17	40	I	5.2
K20	17	46	I	5.7

IF- intermediate filament, PI- isoelectric point

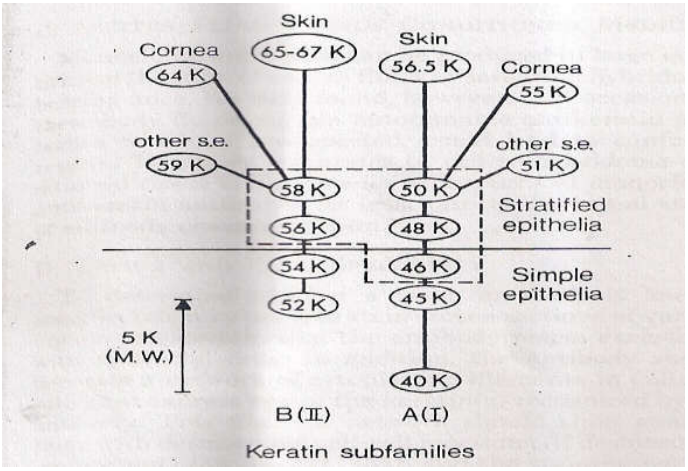
Keratins in epidermal development

Human embryonic epidermal development identifiable by histology, ultrastructure and biochemistry can be divided into a) embryonic period (7-9 weeks) b) epidermal stratification(9-10 weeks) c) follicular keratinization (14 weeks) and d) interfollicular keratinization (24 weeks). Keratins are found as early as the 2-8 cell embryo stage. In the embryonic period, the epidermis is represented by only basal and peridermal cell layers. An intermediate layer without any keratinization is seen in addition, in the epidermal stratification phase. In the follicular keratinization phase, the epidermis stratifies into three layers with the formation of hair follicles which begin to keratinize and trichocytes keratins start to express themselves. [8]

Cytokeratins specificty	Normal tissue
5, 6, 8, 17 and 19	Simple and SSE
1, 5, 6 and 8	Simple and SSE
10	Suprabasal KC in keratinizing SSE
14	Basal KC
13	Suprabasal KC in nonkeratinizing SSE
4	Suprabasal KC in nonkeratinizing SSE

DISCUSSION

Not all keratins are synthesized simultaneously by one cell, rather different types of keratins are expressed during the terminal differentiation, in different stages of development, as well as in epithelia. All epithelia (simple and complex) can be classified based upon cytokeratin expression.[72]



Unifying model of keratin expression[73]

Human keratin genes[5]

Human keratin genes	Type I genes	Type II genes
Total genes	33	34
Functional genes	28	26
Pseudogenes	5	8
Epithelial keratin genes	17	20
Hair keratin genes	11	6

Structure of keratin filaments

All intermediate filament proteins share a common structural organization consisting of a non – α -helical N-terminal head domain, a central α-helical rod domain and a C - terminal tail domain.[1]The head domains of keratins have been subdivided into three parts: the end domains (E1), the variable regions (V1), which differ strongly in size and sequence homology (H1) close to the rod domain. The sequence conservation of H1 is very strong in type II but not in type I keratins. Keratins are heteropolymers consisting of equimolar amounts of type I plus type II keratins. The heteropolymeric nature is imposed at the level of the double - stranded coiled coil.[74]

Binding between keratin intermediate filaments and desmosomal proteins

In epidermal cells, keratin intermediate filaments connect with desmosomes to form extensive cadherin - mediated cytoskeletal architectures. Koulis et al explored the biochemical nature of the connections between keratin filaments and desmosomes in epidermal keratinocytes. They showed that carboxyl terminal “tail” of DPI associates directly with amino terminal “head” of type II epidermal keratins, including K1, K2, K5 and K6. They had engineered and purified recombinant K5 head and DPI tail and demonstrated direct interaction in vitro by solution-binding assays. This marked association is not seen with simple epithelial type II keratins, vimentin or with type I keratins, providing a possible explanation for the greater stability of the epidermal keratin filament architecture over that of other cell types. They identified an 18-amino acid residue stretch in the K5 head that

is conserved only among type II epidermal keratins and that appears to play some role in DPI tail binding.[76]

Structural significance of keratin pairs

Keratin pair refers to co-expressed acidic and basic keratins and does not a priori define a specific level of fibrillar substructure. In human epidermal cells, the 50-kD/ 58-kD keratin pair represents the only keratins synthesized by basal cells, the 56.5-kD/65-67-kD pair is expressed only in suprabasal cells undergoing keratinization and the 48kD/56kD keratin pair is expressed by hyperproliferative keratinocytes in culture and in epidermal diseases 10-nm filament is composed of the 50-kD/58-kD keratin pairs show little tendency towards filament-filament interaction whereas filament enriched in the 56.5-kD / 65-67 kD keratin pair had marked propensity to form dense filament tangles.

Synthesis of keratins

Biosynthesis occurs in 2 phases – In an initial phase, keratin production keeps pace with the increasing rate of total protein synthesis. In second phase, keratin production outpaces total protein synthesis and / or nonkeratin proteins are selectively degraded. In the epidermis, the postulated first phase might occur in the lower strata and the postulated second phase might occur in the upper strata. Only the first phase occurs in the epithelium generated by cultured keratinocytes. Buccal epithelium is characterized by a lack of granular layer and stratum corneum. The concentration of tonofilaments does not increase significantly during the transit to the surface. It is possible that only first phase of keratin biosynthesis occurs in the epithelium and that the second phase does not occur in normal circumstances. Metaplasia of the buccal epithelium involves the acquisition of a normal appearing granular layer and stratum corneum, as though the second phase of keratin biosynthesis were turned on. It is conceivable that certain disorders of keratinization involve disruption to discrete phases of keratin synthesis.[77]

Novel functions of keratin

Since the discovery of keratins, they were considered as molecular meshwork providing structural integrity and resilience to the epithelial cells. P.A .Columbe enlightened that keratin has a regulatory role in translation indirectly. Regulation of such bulk translation, which is a vital process of cell, had significant implications in wound healing. While investigating the expression of keratins as a response to wound, Columbe's group identified Kb6a, and Kb6b and K17 are upregulated in the neighbouring cells close to wound. They observed that Kb6a and Kb6b double knockout embryos do not show delayed wound closure.

Keratin expression in normal tissue

Epithelium: The various epithelia in the human body usually express cytokeratins which are not only characteristic of type of epithelium, but also related to degree of maturation or differentiation within the epithelium. Following cytokeratin phenotypes can be distinguished in different types of epithelia:

Non - Keratinizing Stratified Squamous Epithelia, adneral Structures and Basal Cells: K4-6 (large and basic), K13 (intermediate – sized and acidic), and K14-17(small and acidic) are expressed in non-keratinizing stratified squamous epithelia, including squamous mucosa (mouth, oesophagus, and basal cells). K5 and K14 constitute the keratin network in basal cells and they account for > 10% of the total cellular protein in vivo. [10]

Simple (Glandular) Epithelia*:* K7 and K8 (intermediate-sized and basic) and K18 and K19 (smallest in size and acidic) are exclusively expressed in nearly all simple epithelia, pseudostratified respiratory epithelium and transitional epithelium. K20 (intermediate-sized and acidic).

Keratin Expression in epithelium[1]

Epithelial type	Type I keratins	Type II keratins	distribution
Simple epithelia	8	18	Most secretory and paranchymatous cells
	7	19	Ductal epithelia(bile duct, pancreatic duct and renal collecting duct) and gastrointestinal epithelia
		20	Gastrointestinal epithelia, Merkel cells of the skin and taste buds of oral mucosa
Stratified squamous epithelia	5	14	Basal cells of squamous and glandular epithelia, myoepithelia, mesoepithelia
		15	Squamous epithelia
	8	18,19	Non-cornifying stratified squamous epithelia
Suprabasal cells	1	10/11	Epidermis (entire suprabasal compartment)
		9	Epidermis of palms and soles
	2e		Epidermis(high layers)
	2p		Gingiva, hard palate
	3	12	Corneal epithelia
	4	13	Non-keratinizing stratified squamous epithelia of internal organs
	6	16,17	Hyperproliferative squamous epithelia.

Keratin expression in human neoplasms[1]

Keratin immunohistochemistry has been used in differential diagnosis of epithelial – derived neoplasms from neoplasms of mesenchymal, hemolymphoid or neural crest origin. Keratin immunohistochemistry has also been used to differentiate carcinomas of one origin from another.[1]

Cytokeratin expression in Oral Squamous cell carcinoma

Cytokeratins are diagnostic as well as prognostic marker of SCC. The expression profile of cytokeratin always help in determining of the treatment plan as well as the prognostic outcome. According to Morgan et al, changes observed in the SCC were presence of simple epithelial keratins, K8 and K18, occasionally K7 and reduced expression of differentiation-linked keratins such as K1, K10, K14 and K13 and tendency of down-regulation of primary keratins, K5 and K14.According to Hayden et al, both well and poorly differentiated SCC showed ubiquitous K14 expression involving the infiltrating tumour islands. According to Depondt et al, CK10,19, 18 and 13 are reliable diagnostic and prognostic markers in assessment of oral and pharyngeal SCCs. According to Fillis et al, the expression of CK8/18 in SCC of the oral cavity is an independent prognostic marker and indicated a decreased overall and progression free survival.[49]

Cytokeratin expression in Oral Epithelial Dysplasia

Oral Epithelial Dysplasias acts as a bridge between the normal epithelium and Squamous cell carcinoma in the pathway of malignant transformation. The altered cytokeratins profile

always acts as a helpful tool to understand the transformation of normal oral epithelium to frank carcinoma through dysplasia. According to Lindberg et al, suprabasal K19 staining was correlated to premalignant changes in the oral epithelium. [37]According to Fillis et al, oral leukoplakias with an expression of CK8/18 or CK19 independent of dysplasia, should be resected since they indicated an increased progression potential to invasive SCCs. So the authors suggested from a direct point of view to resect.[50]

Cytokeratin expression in Oral Submucous Fibrosis

Lalli A et al observed an increased expression of K1 and K10 in the suprabasal layers, induction of K6 in the basal layer and complete loss of K19 in the epithelium is noted. Increased expression of K17 in the suprabasal layers correlates with disease severity. K17 expression was completely lost in the basal layer in most severe cases suggesting most risk to undergo malignant transformation.[53]

Keratin expression in carcinomas[1]

Carcinoma of simple epithelial origin	K7, K20 positive	K14, K5/6 negative
Carcinoma of stratified epithelial origin	K14, K5/6 positive	K7,K20 negative
Adenocarcinomas of glandular epithelial origin	K7 positive	
Carcinoma of GIT, genitourinary tract	K7, k20 positive	
Breast carcinoma	K7 positive	K20 negative
Lung carcinoma	K7 positive	K20 negative
Endometrial	K7 positive	K20 negative
Ovarian adenocarcinoma	K7 positive	K20 negative
Thyroid tumours	K7 positive	K20 negative
Colorectal carcinoma	K20 positive	K7 negative
Merkel cell tumour	K20 positive	K7 negative
Gastric adenocarcinoma	K20 positive	K7 negative
Adrenal cortical carcinoma		K7, K20 negative
Prostatic carcinoma		K7, K20 negative
Mesothelioma	K5/6, K8, K18 positive	
Renal cell carcinoma	K19 positive	
Transitional cell carcinoma	K5/K6 positive	
Tumours from epidermis	K14 positive	K8 negative
Tumours from eccrine glands	K8 positive	K14 negative
Basal cell carcinoma	K5/6, K14 positive	
Squamous cell carcinoma	K5/6, K14, K8, K18, K19 positive	
Carcinoma with metastasis	K20 positive	
Oral epithelial dysplasia	K14,K19, K8 positive	K10, K13 negative
Oral Submucous Fibrosis	K1, K10, K6, K17 positive	K19 negative

Cytokeratin expression in Odontogenic tumours and cysts

According to Thelseff et al, keratin is expressed by all types of cells in ameloblastomas as well as epidermoid carcinomas and developing tooth.[54]Hormia et al showed that odontogenic jaw cysts have distinct differences in their cytokeratin content. Only follicular cysts appeared to share the expression of cytokeratin polypeptide no. 18 with ameloblastomas.According to August et al, the combination of FNAB (fine-needle aspiration biopsy) with immunocytochemical determination of CK10 expression by sampled epithelial cells was 100% accurate in distinguishing an OKC from a non - keratinizing odontogenic cysts in series.

Cytokeratin expression in Odontogenic cysts and tumours [59]

Odontogenic cysts and Tumours	Cytokeratin expression
Ameloblastoma	K18 positive
Odontogenic keratocyst	K10, K17, K14, K13 positive
Orthokeratinized odontogenic cyst	K10 positive
Dentigerous cyst	K18 positive

Cytokeratin expression in Salivary gland tumours

Salivary gland tumours can be divided into two major categories: tumours arising from stratified epithelia- pleomorphic adenoma, myoepithelioma, basaloid squamous cell carcinoma, adenoid cystic carcinoma and mucoepidermoid carcinoma and tumours arising from simple epithelia- adenocarcinoma NOS, monomorphic adenocarcinoma, acinar cell carcinoma.[1]According to Dardick et al, distinct differences in the cytokeratin polypeptide complement between normal luminal and myoepithelial cells as well as between luminal and basal cells of Warthin's tumour.

Cytokeratin expression in Salivary gland tumours [61 62]

Stratified Epithelia	
Pleomorphic adenoma	K7,K8, K5/6, K14, K17, K19 positive
Myoepithelioma	K5/6, K14, K17, K19 positive
Adenoid cystic carcinoma	K5/6, K14, K17, K19 positive
Mucoepidermoid carcinoma	K7,K8, K5/6, K14, K17, K19 positive

Simple Epithelia	
Adenocarcinoma NOS	K7, K8, K18 positive, K20 negative
Monomorphic adenoma	K7, K8, K18 positive
Acinic cell carcinoma	K7, K8, K18 positive

Keratin expression in other diseases

Since the function of epidermis are related to skin integrity, skin diseases associated with keratin genes mutations usually show skin bullae, blistering, scaling or hyperkeratosis. In epidemolysis bullosa simplex, the mutations involves both K5 and K14, rendering basal cell less resistant to trauma, resulting in skin fragility. In epidermolytic hyperkeratosis, mutations are found in the highly conserved carboxyl terminal of the rod domain of K1 and the highly conserved amino- terminal of the rod domain of K10[1].

Santos et al demonstrated that that keratin K10 controls epithelial proliferation in skin epidermis *in vivo*.

Keratin mutation and human Mucocutaneous diseases[73]

Keratin	Main expression pattern(s)	Diseases
K1, K10	Suprabasal cells of stratified and cornified epithelia	Bullous congenital icthyosiform erythroderma, epidermolytic hyperkeratosis, diffuse non-epidermolytic palmoplantar keratoderma
K2	Late suprabasal cells of stratified cornified epithelium	Ichthyosis bullosa of Siemens
K3, K12	Cornea-specific keratin	Meesmann's corneal dystrophy
Keratin	**Main expression pattern(s)**	**Diseases**
K4, K13	Mucosa, stratified non-cornified epithelia	White sponge nevus
K5, K14	Basal keratinocytes of epidermis	Epidermolysis bullosa simplex
K6, K16	Palmoplantar , mucosa, wound healing, epidermal appendages	Pachonychia congenital-1, focal non- epidermolytic palmoplantar keratoderma
K7	Myoepithelial cells, simple epithelia	None known
K8, K18	Simple epithelia	Cryptogenic cirrhosis
K9	Palmoplantar epidermis	Epidermolytic palmoplantar

		keratoderma
K15	Basal keratinocytes	None known
K17	Epidermal appendages	Pachyonychia congenital-2
K19	Simple epithelia, epidermal appendages	None known
K20	Gastrointestinal tract epithelia	None known
hHb6, hHb1	Cortical trichocytes	Monilethrix

Future Perspectives

Early concepts of cytoskeleton filaments being passive and rigid mechanical integrators appear to be largely redundant. Cytokerains together with other intermediate filaments, participate in a very dynamic, flexible, highly tissue specific and exiquisitely controlled three-dimensional network transversing the space between the nucleus and the cell membrane[12].A new aspect of cytokeratin biology involves the different proteolytic degradation or cleavage of isolated cytokeratins that may occur in tumours. Cytokeratin 19 fragments (assayed by the Cyfra 21:1 assay) appear in extracellular fluids during malignant diseases. These fragments are supposed to be generated by the proteolytic cleavage of cytokeratins in tumour cells, rendering cytokeratins more soluble. Despite the appearance of cytokeratins in serum as tumour markers, they also are efficient targets for radioimmunolocalization and radioimmunotherapy.More recently there has been considerable interest in the role of cytokeratins during apoptosis. Caspase- mediated cleavage of cytokeratins causes disassembly of the cytoskeleton, formation of pleomorphic cytoplasmic inclusions and stable fragments of cytokeratins. These may be a characteristic feature of epithelial cell apoptosis. Furthermore, this early caspase cleavage event exposes a nonepitope in cytokeratin 18 which is not detectable in non- apoptotic epithelial cells. Antibodies to this non-epitope could therefore be used to specifically recognize apoptotic cells.

Cytokeratin as a prognostic marker

Doweck examined a new tumour marker, Cyfra 21-1, as a prognostic marker in predicting the survival of head and neck cancer patients, and its correlation with clinical outcome. Cyfra 21-1 is a cytokeratin 19 fragment that is recognized by the two monoclonal antibodies BM 19-21 and KS 19-1, which were obtained by immunization of mouse with MCF-7 cells[79].

CONCLUSION

Epithelium - In simple epithelia, Keratins K8, K18, K7, K19 are expressed. In stratified squamous epithelia, keratins K5, K14, K15, K8, K18, K19 are expressed. In suprabasal cells, Keratin K1, K10/11, K9, k12, K13, K6, K16, K17 are expressed. Premalignant lesions and carcinomas - In Squamous cell carcinoma, keratins K5, K6, K14, K8, K18, K19 are expressed.

Oral Epithelial dysplasias express K14, K19, K8. Oral Submucous Fibrosis express K1, K10, K6, K17.Odontogenic cyst and tumours - Odontogenic keratocyst express K10, K17, K14, K13. Dentigerous cyst express K18. Ameloblastoma express K18.Salivary gland tumours - Salivary gland tumours can be divided into two major categories: tumours arising from stratified epithelia-pleomorphic adenoma, myoepithelioma, basaloid squamous cell carcinoma, adenoid cystic carcinoma and mucoepidermoid carcinoma and tumours arising from simple epithelia- adenocarcinoma NOS, monomorphic adenocarcinoma, acinar cell carcinoma. the former express CK 5/6, CK 14, CK17 and CK19 while latter expresses CK7, CK 8 and CK 18.

Mucocutaneous diseases – In Lichen planus, expression of cytokeratins 10, 13, 14 has been altered. In epidemolysis bullosa simplex, the mutations involves both K5 and K14. In epidermolytic hyperkeratosis, mutations are found in K1 and K10. Cytokeratins are diagnostic as well as prognostic marker of normal mucosa, human neoplasms and diseases.

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