Cytokeratin Expression In Health & Disease

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Abstract

Cytokeratins (CK) are the intermediate filament proteins found in epithelia and are expressed in a tissue specific and paired manner. CK pairs comprise of one member each from acidic and basic subfamilies. Oral epithelium is stratified and is an excellent example to illustrate tissue specific CK expression. e.g. Non keratinizing Buccal Mucosa (BM) expresses CK 4, 5, 13 and 14 while keratinizing dorsal tongue expresses CK 1, 2, 5, 6, 10, 14 and 16 or 17. A number of groups have studied CK expression in human oral precancer as well as cancer and some consistent patterns of CK expression have emerged from these studies.

Keywords – Cytokeratins, Cytoskeleton, Hard Keratins, Soft keratins

Introduction

Keratins

The keratins are the typical intermediate filament proteins of epithelia, showing an outstanding degree of molecular diversity.[1] Historically, the term 'keratin' stood for all of the proteins extracted from skin modifications, such as horns, claws and hooves.[2] The word Keratin stems from Greek word Keratos meaning horn.[3] Subsequently, it was realized that this keratin is actually a mixture of keratins, keratin filament-associated proteins and other proteins, such as enzymes. Keratins were then defined as certain filament-forming proteins with specific physicochemical properties and extracted from the cornified layer of the epidermis, whereas those filament forming proteins that were extracted from the living layers of the epidermis were grouped as 'prekeratins' or 'cytokeratins'. Currently, the term 'keratin' covers all intermediate filament-forming proteins with specific physicochemical properties and produced in any vertebrate epithelia. Similarly, the nomenclature of epithelia as cornified, keratinized or non-keratinized is based historically on the notion that only the epidermis of skin modifications such as horns, claws and hooves is cornified, that the non-modified epidermis is a keratinized stratified epithelium, and that all other stratified and non-stratified epithelia are non-keratinized epithelia.[2]

Cytokeratins / Cytoskeleton

A large proportion of the cytoplasm of vertebrate cells, normal or transformed, is represented by components of the cytoskeleton, including actin-containing microfilaments, tubulin-containing microtubules and filaments of intermediate size, with diameters of 7-l 1 nm. First, filaments containing keratin-like proteins ("cytokeratins") are characteristic of epithelial cells. Second, vimentin filaments occur in mesenchymally derived cells, in astrocytes, in Sertoli cells, in vascular smooth muscle cells and in many cultured cell lines. Third, desmin filaments are typical of most types of myogenic cells. Fourth, neurofilaments are typical of neuronal cells. Fifth, glial filaments are typical of astrocytes.[4]

Heteropolymeric filaments are formed by pairing of type I and type II molecules. In humans 54 functional keratin genes exist. They are expressed in highly specific patterns related to the epithelial type and stage of cellular differentiation. About half of all keratins—including numerous keratins characterized only recently—are restricted to the various compartments of hair follicles. As part of the epithelial cytoskeleton, keratins are important for the mechanical stability and integrity of epithelial cells and tissues. Moreover, some keratins also have regulatory functions and are involved in intracellular signaling pathways, e.g. protection from stress, wound healing, and apoptosis.[1]

Cytokeratins/cytoskeleton is a complex dynamic network of protein filaments that reorganizes continuously and extends throughout the cytoplasm. It is responsible for motility, change in shape, muscle contraction, transport of organelles and segregation of chromosomes.[5]

Cytoskeleton depends on three types of proteins:

Actin filaments

Also known as micro filaments, are helical polymers of actin and have a diameter of 5 - 9nm.

They are responsible for cell surface movements and maintain polarity of the cell.

Microtubules

Are long hollow cylinders made of tubulin and have a diameter of 25mm. They aid in positioning of organelles within the cytoplasm.

Intermediate filaments

Are tough ropelike structures and have a diameter of 10nm, in between that of microfilaments and microtubules.[5]

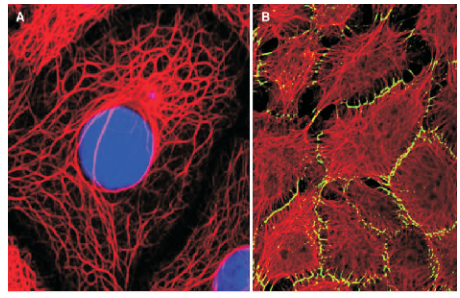


Figure 1 Histophotograph showing Cytoskeleton of epithelial cells. a Nuclei stained in blue, Keratin filaments (in *red*) b desmosomal component desmoplakin (in *green*)[1]

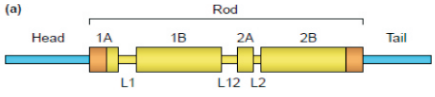
The dynamics of oral mucosa is known for its inherent defensive nature. Certain areas demand tough shield when subjected to mechanical insults. This is met by structural scaffolding material referred as cytoskeleton comprised of intracellular protein filaments called cytokeratins in the surface squames 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.[6]

Cells in an epithelial tissue are anchored to neighbouring cells by a number of distinct adhering type cell junctions. Generally, adhering junctions are composed of a transmembrane component and a variety of cytoplasmic adapter proteins that in turn link cytoskeletal structures to sites of cell – cell contact. Adhesive junction assembly and stability are tightly controlled processes and there must be mechanisms to allow cell to move with respect to their neighbours during normal physiologic processes (eg during normal development and wound healing)[7] Nine human 'hard' type I keratin genes organized as a cluster along with other type I genes on chromosome 17q12–21 have been described. Existence of six functional 'hard' type II keratin genes, clustered in a similar fashion within the type II keratin gene domain on human chromosome 12q13 have been reported. As is the case for the keratin genes expressed in 'soft' epithelia, these hard keratin genes are differentially regulated in the hair producing tissue, which is a mosaic of multiple programs of differentiation.[8]

CK structure and classification

All the CK have a common structure, which consists of a rod domain, or alpha -helix, which is flanked on either side by head and tail domain. The head domain is the amino terminus, while the tail domain is carboxyl terminus. Various CK show 32— 70% homology in the rod domain. Hence, antibodies developed against CK tend to cross-react with many CK polypeptides as also other IF proteins. Thus, the need for the development of monospecific Monoclonal Antibodies arose. Till to-date hundreds of Monoclonal Antibodies have been developed against various CK polypeptides. Many of these are not only specific to a single CK polypeptide, but are also epitope specific.[9]

Figure 2 Figure 2 Introduction to keratin IFs. (a) depicts the tripartite domain structure of all keratin proteins, with a central rod domain dominated by α-helical subsegments (1A, 1B, 2A and 2B) and separated by short linker regions (L1, L12 and L2). The rod is flanked by nonhelical head and tail domains at the amino and carboxyl termini, respectively. The orange boxes depict the position of 15–20 amino acid segments[2]



Cytokeratins constitute the principal component of the cytoskeleton in epithelial cells. They correspond to a group of 19 proteins characterized by their stability and low solubility in physiologic buffer. Using electrophoretic and immunologic techniques with monoclonal antibodies, 2 subfamilies have been classified: the first comprising relatively large basic proteins (56-67 kDa), numbered from 1 to 8; the second comprising smaller more acidic proteins numbered from 9 to 19. Low molecular- weight cytokeratins (40 kDa) are found in glandular and simple epithelium, those of intermediate molecular weight in stratified epithelium, and high molecular- weight cytokeratins (67 kDa) in stratified keratinized epithelium.[10] CK expression is not only differentiation dependent, but is also regulated by certain other factors, such as calcium ion concentration, retinoic acid, etc. Environmental factors, such as changes in the underlying connective tissue, biting force, dental occlusion, etc. are also known to modulate CK expression[11]

Types of Keratin :

1. Based on their structure:

Hard keratin: Cysteine rich keratins are tougher in nature and constitute the 'hard' keratins found in found in nail, hair cortex, hair cuticle[3]; the keratin type seen at these sites have very little flexibility owing to the presence of many cysteine disulfide crosslinks. They differ from the epithelial keratins by their considerably higher sulfur content in their non-helical head and tail domains, which is mainly responsible for the high degree of filamentous cross-linking by keratin associated proteins.[8,12]

Soft keratin: Loosely packed bundles of cytoplasmic keratin filaments in epithelial cells are termed as 'soft or cyto'keratins. Found in the epidermis of skin in the form of flattened non-nucleated scales that slough continually.[3] The disulfide links are fewer in number which allows some stretching but returns to normal upon relaxation of tension.[8,12]

2. Based on X-ray diffraction pattern:

Alpha: The X-ray diffraction pattern of this type resembles that of α-helix with a 5.1 A spacing. The α-helix is right handed and has 3.6 residues per turn. The hydrogen bonding occurs within one polypeptide chain.[12]

Beta: In the X-ray diffraction pattern of this type, periodic repeats were 3.5 and 7 angstroms. The helix is right-handed with an average of 6 residues. The hydrogen bonding occurs between neighboring polypeptide chains.[12]

3. Based on amino acid sequence, keratins are classified into type I and type II:

Type I family includes keratins numbered 9-20 which are composed of acidic proteins, with a molecular weight 40-56 kDa and pI- 4.9-5.4 [9,12]

Type II family includes keratins numbered 1-8 which are composed of basic proteins, with a molecular weight of 52-67 kDa and pI- 6.5-8.5 [9,1]

4. Based on molecular weight:

Low molecular weight keratins: Include keratins with a molecular weight of 40kDa. These keratins are mainly distributed in glandular and simple epithelia.[6,12]

Intermediate molecular weight keratins: Include keratins with a molecular weight intermediate between 40kDa and 57kDa and are found in stratified epithelia.[6,12]

High molecular weight keratins: Include keratins with a molecular weight of 57kDa and are seen in keratinized stratified epithelia.[6,12]

Table 1 The Keratin Nomenclature

Keratin types	Type I	Type II
Epithelial types	K9	K1
	K10	K2
	K12	K3
	K13	K4
	K14	K5
	K15	K6
	K16	K7
	K17	K8
	K18 K19 K20 K23 K24	K76 K77 K79 K80

Table 2 'Hard' and 'Soft' principles pertaining to keratin function and regulators:

'Hard' principles	'Soft' principles
Assembly through heteropolymerization	Role in cell signaling
Dynamic nature	Role as stress proteins
Regulation via posttranslational modifications	Role in regulating the availability of other abundant cellular proteins
Function to protect cells from stress, mechanical as well as non mechanical	Role in assisting protein targeting in polarized epithelia
Mutation associated predisposition or cause of severe human disaeses	Fulfils unique, tissue - specific and context – dependent fuctions
Importance of gene modifiers	
Functional redundancy	

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.[6]

Cytokeratins (CK) are being extensively used as diagnostic markers for various malignancies and other diseases, including human oral precancer and cancer, due to their tissue specific expression. CK are epithelia specific intermediate filament (IF) proteins, which are expressed in a differentiation dependent and tissue specific manner.[9]

Epithelial cells are characterized by intermediate filaments that consist of different combinations of cytokeratins. The profile of suprabasal cytokeratin expression in a particular epithelium is indicative for its degree of differentiation.[13]

Expression of Cytokeratins in Health

Epithelial thickness increases gradually from the skin to the mucosal aspect. The stratified squamous epithelium covering the lip could be divided into: (i) appendage-bearing, orthokeratinised epidermis; (ii) orthokeratinised vermilion which had a more prominent rete pattern than the epidermis; (iii) parakeratinised, PAS-positive intermediate zone; and (iv) non- or parakeratinised labial mucosal epithelium. The CK pattern changes across the intermediate zone, with gradual loss of CK 1 and 10 from the skin, and CK 4, 13 and 19 from the mucosal, aspect. CK 5 and 14 are consistently expressed basally, and variably expressed suprabasally. CK 8, 18 and 20 are negative.[14]

Table 3 Staining patterns of principal cytokeratins (CK) in the stratified squamous epithelium

Layer	CK1	CK10	CK4	CK13	CK5	CK14	CK19
Labial Skin							
S. basale	–	–	–	–	+	+	–
S. spinosum	+	+	–	–	±	–	–
S. granulosum	+	+	–	–	–	–	–
S. corneum	–	–	–	–	–	–	–
Vermilion							
S. basale	–	–	–	–	+	+	–
S. spinosum	+	+	–	–	±	±	–
S. granulosum	+	+	–	–	±	±	–
S. corneum							
Intermediate Zone							
S. basale	–	–	–	–	+	+	±
S. spinosum	±	±	±	±	±	±	±
S. corneum	–	–	–	–	–	–	–
Labial mucosa							
S. basale	–	–	–	–	+	+	+
S. spinosum	±	–	+	+	±	±	±

covering labial skin, vermilion, intermediate zone and labial mucosa

(-) Negative staining; (+) positive staining; (±) positive staining (with variable intensity) or negative staining. Positive controls were: CK 1 and 10, suprabasal keratinocytes in abdominal epidermis and palatal mucosa; CK 4 and 13, suprabasal keratinocytes in nonkeratinised cheek mucosal stratified squamous epithelium; CK 5 and 14, basal keratinocytes; CK 19, basal keratinocytes of gingival and cheek mucosal stratified squamous epithelium, outer root sheath of hair follicles, and luminal cells lining the ducts of sweat and minor salivary glands

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. [6,12]

KFAPs in oral epithelia: [6,12]

Class of KFAP Example

Class I Filaggrin

Class II Trichohyalin

Class III Loricrin

Table 4: Staining patterns of filaggrin, loricrin and involucrin in the stratified squamous epithelium

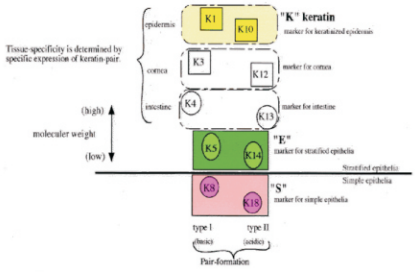
Layer	Profilaggrin/	Locricrin	Involucrin
Labial skin			
S. basale	-	-	-
S. spinosum	-	-	-
S. granulosum	+	+	+
S. corneum	-	-	-
Vermilion			
S. basale	-	-	-
S. spinosum	-	±	±
S. granulosum	+	+	+
S. corneum	-	-	-
Intermediate zone			
S. basale	-	-	-
S. spinosum	-	±	+
S. corneum	-	-	-
Labial mucosa			
S. basale	-	-	-
S. spinosum	-	-	+

covering labial skin, vermilion, intermediate one and labial mucosa

(-) negative staining ; (+)positive; (+) positive staining (with variable intensity) or negative staining. Positive controls were stratum granulosum of epidermis.

Keratinized epithelium like that from skin is highly differentiated and expresses the larger cytokeratins 1 and 10. In contrast, the simple and glandular epithelia express the smaller cytokeratins 7, 8 and 18. The cytokeratin expression in skin epithelium, normal oral epithelia and respiratory epithelia has been well investigated. The basal layers of these epithelia usually express the cytokeratins 5 and 14. In the suprabasal layers of the masticatory mucosa the cytokeratins 1 and 10 are found (like in skin) but also 6 and 16. The lining mucosa of the oral cavity is characterized by suprabasal expression of the cytokeratins 4 and 13, which is also typical for the oropharyngeal mucosa.[13]

Human oral cavity is the best example to illustrate differentiation dependent expression of CK by stratified epithelia. Various sites in the human oral cavity show different levels of differentiation and keratinization and accordingly their CK expression varies. All the sites in the human oral cavity express CK pair of 5 and 14, on which the expression of other CK pairs like CK 1 and 10 and CK 4 and 13 is super imposed. For example, buccal mucosa which is a non keratinizing epithelium expresses CK pair of 4 and 13 along with CK 5 and 14, while gingiva which is a keratinizing epithelium



expresses CK 1 and 10 along with CK 5 and 14[9]

Figure 3 Distribution of Keratin[11]

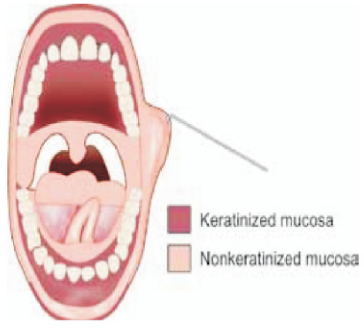


Fig. 1: Keratinization in oral mucosa

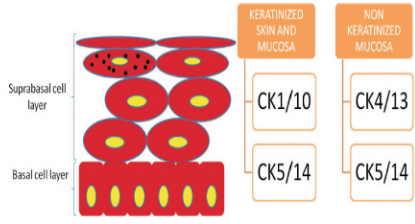


Figure 4 Schematic diagrams showing keratinized mucosa and non keratinized mucosa of oral cavity[3]

Cytokeratins Expression	*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

Table 5 Normal Cytokeratin Expression In Salivary Epithelia And Odontogenic Tissues

Cytokeratins antibodies: use in basic research -

CK on one hand are connected to nuclear envelope, while on the other hand they interact with plasma membrane proteins. The membrane proteins in turn interact with the ECM (extra cellular matrix) proteins. Thus, it is believed that CK are also involved in transduction signals and transport of nutrients from inside to outside the cell and vice a versa. Usually the amino terminus of the CK interacts with the carboxyl terminus of the membrane proteins. These are very complex interactions and have gained importance in tumour biology. Epitope specific Monoclonal Antibodies have an important role in the study of these interactions. The interactions of CK with other cellular proteins are an important area of basic research: particularly, the involvement of CK in cell—cell and cell—ECM (Extra Cellular Matrix) interactions and signaling.[9] Although very little is known about the exact role of CK in signaling, a large amount of literature shows the importance of CK and their interactions with, membrane proteins like integrins, Bullous pemphigoid antigens and other cytoskeletal proteins.[6,9] A review of literature suggests that a large number of groups are working in this field worldwide. These studies require the use of not only monospecific but epitope specific antibodies. In basic research on cell structure, function and cellular differentiation, antibodies to CK can serve as fine and sensitive analytical tools. Confirmation specific and phosphorylation specific MAb are also of significance in these studies.[9]

Expression of Cytokeratins in Disease –

Differences in CK expression have been shown between some Squamous Cell Carcinomas and their normal counterparts.[16] According to study done by Vaidya et al, differentiation dependent alterations in CK expression in Squamous Cell Carcinomas (SCC) of the buccal mucosa (BM). These alterations were of two types. (1) Aberrant expression of certain CKs not expressed in the normal tissue; and (2) non-expression (or down regulation) of certain CKs which are expressed in the normal tissue. They observed loss of basic keratins CK 5 and 14 and aberrant expression of simple epithelial keratins occurs during malignant transformation of the human oral mucosas.[16] In a study done by C Li et al , in Warthin's tumour, keratins 7, 8, 18 and 19 were consistently detected in the epithelial cells of the tumour, a profile with a tendency to mimic the same in normal ductal epithelium.[17] In study conducted by S Boisnic et al, in Buccal Mucosa Lichen Planus expression of cytokeratins 1,2,10 and 11 with decreased expression of CK 4 and 13 and moderate increase in CK 6,16, 17 and 19 was reported. In case of Gingival Lichen planus, decreased expression of CK 1, 2, 10, 11and 13 was observed.[18]

Normal human adult tongue expresses CK 1, 2, 4, 5, 6, 10, 13, 14 and 16 and occasionally 17. CK 5 and 14 are found only in the basal layer

of both fungiform and filiform papillae. CK 1 and 10 are seen in spinous and granular layers of fungiform and filiform papillae. CK 4 and 13 are expressed in the spinous and granular layers of filiform papillae only. CK16 is found in spinous, granular and cornified layers of fungiform papillae and all the layers of filiform papillae, although the intensity varies from layer to layer.[19]

Table 6: Expression of Cytokeratins in Oral Carcinoma / Pre cancerous lesion and condition

Oral carcinoma / Pre cancerous lesion / condition	Expression of CK
Squamous Cell Carcinoma Well differentiated SCC	CK 4 + ve CK 13 +ve coexpressed with CK 1 +ve and CK 10 +ve CK 19+ve CK 5 –ve, CK 14-ve
Moderately differentiated SCC	CK 4 CK 13 is substituted by CK 1 CK 10
Poorly Differentiated SCC	Differentiation keratins absent
OSMF	CK 1 +ve CK10 +ve CK5 +ve CK14 +ve
Lichen Planus On Buccal Mucosa	CK 1+ve CK 2+ve CK10+ve CK11+ve CK4-ve CK13 –ve CK 6 +ve CK 16 +ve CK 17 +ve CK 19 +ve
On Gingiva	CK 1 +ve CK 2+ve CK 10 +ve CK 11 +ve CK 13 +ve
Epithelial Dysplasia Mild	CK 1 +ve CK 10 +ve CK 4 +ve CK 13 +ve
	CK 1 and completely replace CK 4 and 13, CK 19
Severe	CK 1 -ve CK 10 –ve CK 4 –ve CK 13 –ve CK 19 +ve

Table 7: Expression of Cytokeratins in Odontogenic Cysts

Odontogenic	CK 19	CK 17	CK 5	CK 6	CK 7	CK 10	CK 20
Odontogenic Keratocyst	-	+	+	+	-	+	-
Dentigerous	+	-	+	+	+	±	-
Radicular Cyst	+	-	+	+	-	±	-

Table 8 : Cytokeratin expression in odontogenic tumors

Odontogenic tumour	Expression of CK
Adenomatoid odontogenic tumour (AOT)	CK 14
Ameloblastoma	CK 13 CK 14 CK 19
Calcifying epithelial odontogenic tumour (CEOT)	CK 14 CK 7 CK 13 CK 19
Ameloblastic fibroma	CK 13 CK 14 CK 7
Odontoma	CK 7 CK 14
Warthin's Tumour	CK 7 CK 8 CK 18 CK 19

Conclusion

Cytokeratins play an important role in molecular progression of certain diseases, their embryological development and lineage. A number of groups have studied CK expression in human oral precancer as well as cancer and some consistent patterns of CK expression have emerged from these studies. To list a few, anomalous expression of CK 1 and or 10 in well-differentiated tumours developed from non keratinizing tissue like buccal mucosa; down regulation of differentiation specific CK like CK 1 & 10 and CK 4 &13 in the supra basal layers of both precancerous lesions and SCC and simultaneous appearance of basal CK like 5 and 14 in supra basal layers; aberrant expression of simple epithelia specific CK 8 and 18. Thus in conclusion it appears that CK and their associated proteins can be used as prognostic marker in oral cancer.

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