

# Expression of Cytokeratins in Health and Disease

Dr. Medha Deora

PG Student

Department of Oral Pathology

Institute of Dental Studies & Technologies

N H - 58, Delhi-Meerut Road, Modinagar-201201 (U.P.)

## 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.

**Keywords :** Cytokeratins, Monoclonal Antibodies.

## Introduction

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.<sup>1</sup> 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.<sup>2</sup>

## 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.<sup>1</sup>

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.<sup>3</sup> 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.<sup>4</sup>

## 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.<sup>5</sup>

**Table 1** Staining patterns of principal cytokeratins (CK) in the stratified squamous epithelium covering labial skin, vermilion, intermediate zone and labial mucosa

Layer	CK1	CK10	CK4	CK13	CK5	CK14	CK19
<b>Labial Skin</b>							
S. Basale	-	-	-	-	+	+	-
S. Spinosum	+	+	-	-	±	-	-
S. Granulosum	+	+	-	-	-	-	-
S. Corneum	-	-	-	-	-	-	-
<b>Vermilion</b>							
S. Basale	-	-	-	-	+	+	-
S. Spinosum	+	+	-	-	±	±	-
S. Granulosum	+	+	-	-	±	±	-
S. Corneum	-	-	-	-	-	-	-
<b>Intermediate Zone</b>							
S. Basale	-	-	-	-	+	+	±
S. Spinosum	±	±	±	±	±	±	±
S. Corneum	-	-	-	-	-	-	-
<b>Labial mucosa</b>							
S. Basale	-	-	-	-	+	+	+
S. Spinosum	±	-	+	+	±	±	±

(-) Negative staining; (+) positive staining; (±) positive staining (with variable intensity) or negative staining.<sup>5</sup>

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.<sup>2</sup>

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<sup>1</sup>

## 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 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. 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. 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.<sup>1</sup>

#### Expression of Cytokeratins in Oral disease

Differences in CK expression have been shown between some Squamous Cell Carcinomas and their normal counterparts.<sup>6</sup> 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 basal keratins CK 5 and 14 and aberrant expression of simple epithelial keratins occurs during malignant transformation of the human oral mucosae.<sup>6</sup> 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.<sup>7</sup> In study conducted by S Boinsic et al, in Buccal Mucosa Lichen Planus, expression of cytokeratins 1, 2, 10 and 11 can be observed while decreased expression of cytokeratin 4 and 13. Further they have also reported moderate increase in cytokeratins 6, 16, 17 and 19. In case of Gingival Lichen planus, decreased expression of cytokeratin 1, 10, 11 and 13 was observed.<sup>8</sup>

#### 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 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.

#### References

1. Upasani OS, Vaidya MM, Bhisey AN. Database on monoclonal antibodies to Cytokeratins. *Oral Oncology* 2004; 40: 236-56
2. Guo J H, Maltha JC, San G et al. Cytokeratin expression in palatal and marginal mucosa of cleft palate patients. *Archives of Oral Biology* 2006; 51: 573-80
3. Mira BG, Sebastián JVB et al. Expression of cytokeratins in epithelialized periapical lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009; 107 (4): e43-e46.
4. Vaidya M M, Sawanta S S, Borgesb A M et al. Cytokeratin expression in precancerous lesions of the human oral cavity. *Oral Oncology* 1998; 34: 261-4.
5. Barrett AW, Morgan M, Nwaeze G, Kramer G, Berkovitz BKB. The differentiation profile of the epithelium of the human lip. *Archives of Oral Biology* 2005; 50: 431-8.
6. Vaidya M M, Borges A M, Pradhan S A, Bhisey S A. Cytokeratin Expression in Squamous Cell Carcinomas Tongue and Alveolar Mucosa. *Oral Oncol, Eur J Cancer* 1996; 328 (5): 333-6.
7. Li C, Okamoto Y, Ohmura H, Ogawa K et al. Expression of Cytokeratins in Warthin's Tumour (Adenolymphoma) of Parotid Glands: Specific Detection of Individual Cytokeratin Types by Monoclonal Antibodies. *Oral Oncol* 1996; 32 (5): 352-8.
8. Boinsic S, Ouhayoun JP et al. Alteration of cytokeratin expression of the Oral Lichen Planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; 79: 207-15.

## Ethics for Dentistry which are Forgotten

**Dr. Naresh Sharma**

Asst. Professor

Dept. of Pedodontics & Preventive Dentistry, Manav Rachna Dental College, Faridabad, INDIA

**Dr. Mehak**

Intern

#### Introduction

**E**thics is the philosophy of human conduct, a way of stating and evaluating principles by which problems of behaviour can be solved. Recently in the T.V show an episode was screened it got lot of flak from medical/dental organization. It was seen that due to ignorance on part of few professional the whole medical fraternity was shown in bad light.

In India the dentist are in every street in every neighbourhood, the pressure is much more. For this in India the dentist act was amended via 17A empowering the dental council of India to prescribe standards of professional conduct and etiquette.

Dental ethics is also closely related to law. In most countries there are laws that specify how dentists are required to deal with ethical issues in patient care and research. Usually the requirements of dental ethics and law are similar. But ethics should not be confused with law. One difference between the two is that laws can differ significantly from one country to another while ethics is generally applicable across national boundaries.

In the rural area the dentist: population ratio is 1:250,000 and in urban area the ratio is 1:10,000. This ratio is because of more than three-fourth of the dentist are clustered in urban area, this could be attributed to relatively high fees towards dental treatment, dental knowledge and the importance of oral health in the urban areas only.

Dental profession in India is regulated by the dental council of India and is financed by the ministry of health and family welfare, government of India. Ethics and resolution of the ethical problems have traditionally been addressed through the use of passed down act or statement that have been developed over a time through a unwritten protocol established and accepted by various professional clinicians.

Following are the some regulations which are commonly trespassed.

The code of ethics was formed by the dental council in 1975 and later notified by the government of India as dentist (code of ethics) regulation 1976 following are considered to be unethical practices:

1. Practice by unregistered persons employed by the dentist.
2. Dentist signed under his name and authority issuing any certificate which is untrue, misleading or improper.
3. Dentist advertising whether directly or indirectly for the purpose of obtaining patient or promoting his own professional advantage and the use of such words as teeth, painless extraction or flickering light sign showing any matter other than his name and qualifications.
4. Use of bogus diplomas etc.
5. Allowing commission.
6. Paying or accepting commission.

7. Undercutting of charges in order to solicit patient.

8. If consulted the dentist accepts charge of the case without request of the referring dentist.

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#### Conclusion

Rules and regulation are not followed effectively by dental practitioner in their clinical practice. A profession consists of a limited group of persons who have acquired some special skill and are therefore able to perform the function in the society better than the average person.

A professional person is expected to have respect for human beings, competence in his chosen field, integrity, and primary concern with service rather than with prestige or profit. Creating awareness amongst colleagues is our responsibility, and following them is theirs. As far as ethics and moral are concerned it only advisable that one goes for self regulation to ensure that the dignity and honour of the profession is maintained.

Ethical codes are important in developing higher standards of conduct for they are based upon what is considered to be the correct attitude and the correct procedure.