ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 10 | October - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

# CYTOKERATINS: NOT AN EPITHELIAL ENTITY ANYMORE?

Oral Pathology

**Dr. Geetpriya Kaur** Associate Professor, IDST Dental College, Meerut.
**Dr. Devicharan Shetty** HOD, Department of Oral Pathology, ITS Dental College, Murad Nagar.
**Dr. Seema Sikka** Consultant, Paradise Diagnostics.
**Dr. Aparna Pathak** Consultant, Paradise Diagnostics.

## ABSTRACT

Cytokeratins are proteins of keratin-containing intermediate filaments found in the intracytoplasmic cytoskeleton of epithelial cells. Cytokeratins are represented in epithelial tissue by at least 20 different polypeptides. They range in molecular weight between 40KDa and 60KDa and isoelectric pH between 4.9-7.8. The individual cytokeratin polypeptides are designated 1 to 20. Cytokeratin 1 has the highest molecular weight and highest isoelectric pH, while CK19 has the lowest molecular weight and a low isoelectric pH. Cytokeratins are divided into type I and type II subgroups. The detection of cytokeratins in neoplasms by immunohistochemistry has numerous diagnostic and investigative applications. The patterns of cytokeratin expression in the normal epithelium, as well as their altered expression in premalignant lesions and malignancies, might suggest newer diagnostic improvements for positive patient outcomes.

## KEYWORDS

Cytoskeleton, Intermediate filaments, Cytokeratin, Immunohistochemistry

## INTRODUCTION

The oral cavity consists of various cells that maintain structural integrity and functional capacity. The cells possess a cytoskeleton, a network of filaments that provides the structural framework as well as anchors all organelles to the cellular membranes. The intermediate-sized filaments of epithelial cells are composed of a family of water-insoluble proteins termed cytokeratins (CKs).[1]

In 2004, Rogers et al. demonstrated that humans possess a total of 54 functional keratin genes, i.e 28 type I and 26 type II CKs, forming two clusters of 27 genes each on chromosomes 17q21.2 and 12q13.13 (the gene for the type I keratin CK18 being located in the type II keratin gene domain.[2]

**Table – 1 Human Cytokeratin Genes**

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

**Source:** Schweizer J et al.[2]

## STRUCTURE OF CYTOKERATIN FILAMENTS

All intermediate filament proteins display a common structural framework comprising a non – α – helical N-terminal head domain, a central α-helical rod domain, and a C – terminal tail domain.[3] The head domains have been further classified into three types: E1- end domains; V1- variable regions, and H1- sequence homology closer to the rod domain. However, the sequence conservation of H1 is very strong in type II keratins but not in type I.[4]

## SIGNIFICANCE OF CYTOKERATIN PAIRS

The CK pair refers to co-expressed acidic and basic keratins. Moreover, in human cells, the 50-kD/58-kD CK pair represents the CKs synthesized by basal cells, while the 56.5-kD/65-67-kD pair is observed in suprabasal cells with keratinization. The 48kD/56kD CK pair is demonstrated by hyperproliferative keratinocytes in cultures and diseased states.[1]

## CYTOKERATIN EXPRESSION IN NORMAL TISSUES

**Epithelium:** Following phenotypes of CK phenotypes can be differentiated into different types of epithelium:

1) **Keratinizing epidermis**: CKs1 and 2 have been demonstrated in the keratinizing epidermis and the epithelium from the anal canal as well as the ectocervix.[5]

2) **Non-keratinizing stratified squamous epithelia, adnexal structures, and the basal cells**: CKs4-6 (large and basic), CK13 (intermediate-sized and acidic), and CKs14-17 (small and acidic) are expressed in non-keratinizing stratified squamous epithelia. Although CK5 and CK14 are seen in basal cells, the exit of cells from the basal layer initiates the expression of CKs1 and 10.[6]

3) **Simple (glandular) epithelia**: CKs7 and 8 (intermediate-sized and basic) along with CK18 and CK19 (smallest in size and acidic) are exclusively expressed in simple epithelia, pseudostratified respiratory epithelium, and transitional epithelium. CK20 (intermediate-sized and acidic) is observed in the gastric foveolar epithelium, intestinal villi, taste buds, and umbrella cells of the transitional epithelium.[5]

## CYTOKERATIN EXPRESSION IN DISEASED STATES

CK immunohistochemistry has been employed for obtaining a differential diagnosis of epithelial-derived neoplasms from neoplasms of mesenchymal, hemolymphoid, or neural crest origin.

1) **Oral squamous cell carcinoma (SCC)**: Reduced expressions of secondary CKs – 1, 10, 4, and 13 are observed in well-differentiated SCC that are localized in the prickle and central cells of the tumour islands. Neoplastic cells often co-express both sets of CKs1, 10, 4 & 13. However, in less differentiated SCCs, fewer clusters of epithelial cells contain these keratins.[7]

2) **Oral epithelial dysplasia**: Increased expressions of CK5 and CK14 beyond the basal layer have been demonstrated by immunohistochemistry. This is in accordance with the presence of basal cell hyperplasia and decreased expressions of differentiated CKs-1, 10, 4, and 13. Sometimes, increased expression of 'fast cell turnover' cytokeratins, CKs6 and 16, is displayed in the dysplastic epithelium or clinical leukoplakia irrespective of the presence of dysplasia.[8]

3) **Oral submucous fibrosis**: Increased expressions of CK1 and CK10 in the suprabasal layers, CK6 induction in the basal layer, and absence of CK19 in the epithelium are observed. Additionally, the increased expression of CK17 in the suprabasal layers correlates with the disease severity.[7]

4) **Odontogenic tumors and cysts**: Originating from the odontogenic epithelium, they express basal cell cytokeratins CKs5, 10, 13, and 14, but do not demonstrate staining of CKs7, 8, 18, and 20. However, CK19 is also frequently expressed in odontogenic myxoma and clear cell odontogenic carcinoma. Craniopharyngioma and ameloblastoma of the jaw express CK13 and suggest a related embryonic origin.[3] Dentigerous cysts reveal the presence of CK18 whereas odontogenic keratocysts may stain with CK17 due to the presence of metaplastic, or more poorly differentiated, squamous cells.[3,7]

5) **Salivary gland tumors**: Salivary gland tumors can be divided into two groups: tumors arising from stratified epithelia-pleomorphic adenoma, myoepithelioma, basaloid squamous cell carcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma and tumors arising from simple epithelial cells-adenocarcinoma not otherwise specified, monomorphic adenocarcinoma, acinar cell carcinoma. The first group express CKs 5/6, CK 14, CK17, and CK19, while the latter expresses CK7, CK 8, and CK 18. Pleomorphic adenoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma display focal positivity for CKs7 and CK8, which might differentiate them from basaloid squamous cell carcinoma. Furthermore, benign or malignant myoepithelioma, adenoid cystic carcinoma, and pleomorphic adenoma demonstrate CK14 staining due to myoepithelial cell components. Additionally, salivary gland adenocarcinoma also shows positivity for CK7, 8, and 18 and is negative for CK20.[7]

**c) Mucocutaneous diseases**:
Several skin diseases associated with keratin gene mutations display skin bullae, blistering, or hyperkeratosis. Epidermolysis bullosa simplex shows staining with CK5 and CK14, as less resistant basal cells result in skin fragility. Epidermolytic hyperkeratosis shows mutations in the highly conserved carboxyl terminal of CK1 and the highly conserved amino terminal of CK10. Furthermore, oral lichen planus shows positive expressions for CKs10, 13, and 14.[7]

## NEGATIVE CYTOKERATIN EXPRESSION IN DISEASED STATES

**Table – 2 Cytokeratin Negative Tumors**

| Studies | Tumor | Cytokeratin Expression |
|---|---|---|
| Hurtuk et al.[9] | Malignant mesothelioma | CK 7- Negative |
| Chu et al.[10] | Adrenal cortical carcinoma, germ cell tumor, prostate carcinoma, renal cell carcinoma, and hepatocellular carcinoma | CK 7- Negative<br>CK 2- Negative |
| Terada et al.[11] | Small cell lung carcinoma | CK 5/6, 7,8,14,18 - Negative |
| Lu et al.[12] | Breast cancer | CK 7- Negative |
| Miner et al.[13] | Merkel cell carcinoma | CK 20- Negative |

Figure 2: Cytokeratin-negative tumors

It is still ambiguous that negative expression of CK might be a result of independent neoplastic mechanisms or associated with epithelial-mesenchymal transition. Aberrant expression caused by various inflammatory mechanisms might produce false positive CK expressions in such cases. Thus, other epithelial markers can be used in conjunction with CKs to diagnose malignant tumors which show negative CK expression.

## CYTOKERATIN EXPRESSION AFTER EPITHELIAL-MESENCHYMAL TRANSITION

Kim et al. revealed positive expression of CK in gastrointestinal stromal tumors and suggested that this abnormal expression might be due to atypical synthesis of CK by tumor cells or cross-reactivity with other filament proteins.[14] Another study suggested that circulating (CK+) epithelial cells having an epithelial-mesenchymal transition phenotype might induce tumor expansion in patients with clinically undetectable metastases.[15]

Zeng et al. discovered that increased CK17 expression induced apoptosis by elevating Caspase3 levels. Furthermore, dysregulated CK17 expression enhanced pancreatic cancer cell migration and invasion, hence suggesting that CKs might display tumor suppressing potential in various malignancies.[16] Hence, differentiation in such cases can be made by utilizing clinical findings, diagnostic histologic features, and supportive diagnostic markers.

## CONCLUSION

Although the cytokeratin expression is generally confined to epithelia and their neoplasms, their highly diverse expressions can be further associated with epithelial differentiation levels and allow precise assessment of different subtypes. Although they are extremely important for maintaining epithelial integrity, cell signaling, and growth along with protein synthesis, however, recent studies have shown that cytokeratins can now be used as prognostic markers depicting malignant potential as well as treatment receptiveness.

## REFERENCES:


1) Eichner, R., Sun, T. T., & Aebi, U. (1986). The role of keratin subfamilies and keratin pairs in the formation of human epidermal intermediate filaments. *The Journal of Cell Biology*, 102(5), 1767–1777. https://doi.org/10.1083/ jcb.102. 5.1767
2) Schweizer, J., Bowden, P. E., Coulombe, P. A., Langbein, L., Lane, E. B., Magin, T. M., Maltais, L., Omary, M. B., Parry, D. A., Rogers, M. A., & Wright, M. W. (2006). New consensus nomenclature for mammalian keratins. *The Journal of cell biology*, *174*(2), 169–174. https://doi.org/10.1083/jcb.200603161
3) Chu, P. G., & Weiss, L. M. (2002). Keratin expression in human tissues and neoplasms. *Histopathology*, *40*(5), 403–439. https://doi.org/10.1046/j.1365-2559.2002 .01387.x
4) Hatzfeld, M., & Burba, M. (1994). Function of type I and type II keratin head domains: their role in dimer, tetramer and filament formation. *Journal of cell science*, *107 ( Pt 7)*, 1959–1972. https://doi.org/10.1242 /jcs.107.7 .1959
5) Moll, R., Franke, W. W., Schiller, D. L., Geiger, B., & Krepler, R. (1982). The catalog of human cytokeratins: patterns of expression in normal epithelia, tumors and cultured cells. *Cell*, *31*(1), 11–24. https://doi.org/10.1016/0092-8674 (82) 90400-7
6) Schermer, A., Jester, J. V., Hardy, C., Milano, D., & Sun, T. T. (1989). Transient synthesis of K6 and K16 keratins in regenerating rabbit corneal epithelium: keratin markers for an alternative pathway of keratinocyte differentiation. *Differentiation; research in biological diversity*, *42*(2), 103–110. https://doi.org/10.1111/j.1432-0436.1989 .tb00611.x
7) Chatterjee S. (2012) CYTOKERATINS IN HEALTH AND DISEASE. *Oral & Maxillofacial Pathology Journal*, 3(1), 198-202.
8) Hutton, E., Paladini, R. D., Yu, Q. C., Yen, M., Coulombe, P. A., & Fuchs, E. (1998). Functional differences between keratins of stratified and simple epithelia. The Journal of cell biology, 143(2), 487–499. https://doi.org/10.1083/jcb.143.2.487
9) Hurtuk, M. G., & Carbone, M. (2004). A cytokeratin- and calretinin-negative staining sarcomatoid malignant mesothelioma. *Anticancer Research*, *24*(5B), 3097–3102.
10) Chu, P., Wu, E., & Weiss, L. M. (2000). Cytokeratin 7 and cytokeratin 20 expression in epithelial neoplasms: a survey of 435 cases. *Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc*, *13*(9), 962–972. https://doi.org/10.1038/modpathol.3880175
11) Terada T. (2011). Cytokeratin-negative small cell lung carcinoma. *Rare tumors*, *3*(4), e38. https://doi.org/10.4081/rt.2011.e38
12) Lu, S., Yakirevich, E., Wang, L. J., Resnick, M. B., & Wang, Y. (2019). Cytokeratin 7-negative and GATA binding protein 3-negative breast cancers: Clinicopathological features and prognostic significance. *BMC cancer*, *19*(1), 1085. https://doi.org/10.1186/s12885-019-6295-8
13) Miner, A. G., Patel, R. M., Wilson, D. A., Procop, G. W., Minca, E. C., Fullen, D. R., Harms, P. W., & Billings, S. D. (2015). Cytokeratin 20-negative Merkel cell carcinoma is infrequently associated with the Merkel cell polyomavirus. *Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc*, *28*(4), 498–504. https://doi.org/10.1038/modpathol.2014.148
14) Kim, S. S., Choi, Y. D., Lee, J. H., & Choi, C. (2014). Cytokeratin-positive gastrointestinal stromal tumor of biphasic morphology: a case report. *Korean journal of pathology*, *48*(5), 375–378. https://doi.org/10.4132/KoreanJPathol.2014.48.5.375
15) Kallergi, G., Papadaki, M. A., Politaki, E., Mavroudis, D., Georgoulias, V., & Agelaki, S. (2011). Epithelial to mesenchymal transition markers expressed in circulating tumour cells of early and metastatic breast cancer patients. *Breast cancer research: BCR*, *13*(3), R59. https://doi.org/10.1186/bcr2896
16) Zeng, Y., Zou, M., Liu, Y., Que, K., Wang, Y., Liu, C., Gong, J., & You, Y. (2020). Keratin 17 Suppresses Cell Proliferation and Epithelial-Mesenchymal Transition in Pancreatic Cancer. Frontiers in medicine, 7, 572494. https://doi.org/10.3389/fmed.2020.572494