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REVIEW ARTICLE

KERATINS OR CYTOKERATINS – A REVIEW ARTICLE

Praveen Awasthi[1], Amit Thahriani[2], Amritaksha Bhattacharya[2]

[1]Department of Oral Surgery, Career Institute of Dental Sciences, Lucknow, [2]Department of Oral Pathology, Saraswati Dental College, Lucknow- 226001

ABSTRACT:
Epithelial tissues function to protect the organism from physical, chemical, and microbial damage and are essential for survival. To perform this role, epithelial keratinocytes undergo a well-defined differentiation program that results in the expression of structural proteins which maintain the integrity of epithelial tissues and function as a protective barrier. This review focuses on structural proteins of the epidermis and oral mucosa. Keratin proteins comprise the predominant cytoskeletal component of these epithelia. Keratin filaments are attached to the plasma membrane via desmosomes, and together these structural components form a three dimensional array within the cytoplasm of epithelial cells and tissues.
Key words: Cell, cytokeratins, cytoskeleton, keratin.

Corresponding author: Dr. Praveen awasthi, Department of Oral Surgery, Career Institute of Dental Sciences, Lucknow, E mail: awasthinsyak@gmail.com

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INTRODUCTION

The cell is a basic structural and functional unit of body. Cells have a variety of organelles, which help in its vital functions. The various cells, tissues and organs that comprise the oral cavity and related structures are complex entities. One such entity that is physically associated with molecules involved in chemically signaling is the cytoskeleton, which along with extracellular matrix and nuclear matrix governs the shape of the cell and alterations in the organization of genes.

Cells possess a cytoskeleton that provides the structural framework. It facilitates intracellular transport, supports cell junctions, transmits signals about cell contact and permits motility. The cytoskeleton is a complex network of filaments that influence the dynamic morphology of eukaryotic cells in their tissue environment. It maintains the structural integrity of cells, anchoring intra-cytoplasmic organelles to the cellular membranes. The three structural elements of the cytoskeleton are microfilaments, microtubules and intermediate filaments, all are dynamic structures assembled from protein sub-unit and disassembled as cellular activities and external influences on cell changes.

Microfilaments are 6- 8 nm (60 Å) in diameter and consists of globular actin molecules polymerized in to long filaments.

Microtubules are tubular or cylindrical structures with an average diameter of 25nm (150 Å) in diameter, they consist of the protein tubulin.

Intermediate filaments are approximately 10 nm(100 Å) in diameter and have diverse protein composition. They are not contractile but are

important in maintaining the cell shape, contact between adjacent cells and between the cell and extracellular matrix.

Keratins are filamentforming proteins of epithelial cells and are essential for normaltissue structure and function. Keratin genes account for most of the intermediate filament genes in the human genome, making up the two largest sequence homology groups, type I and II, of this large multigene family. They are highly differentiation specific in their expression patterns, implying functional differences.

Cytokeratins, a complex multigene family of proteins, are intermediate filament keratins specifically expressed by epithelial cells. The epithelial keratins or cytokeratins (CK) constitute a family of 20 polypeptides distinguishable by their molecular weight, isoelectric point, X-ray diffraction pattern and also as hard and soft keratin. They are divided into two main groups:

Type 1 (CK 9–20), which are smaller and acidic polypeptides.

Type 2 (CK 1–8), larger and basic-neutral polypeptides.

CYTOSKELETON

The term cytoskeleton derives from **''cyto''** (kutos in Greek meaning ''hollow vessel'') and **''skeleton''** (skeletos in Greek meaning''dried up'').The mammalian cell cytoskeleton consists of a diverse group of fibrillar elements that play a pivotal role incell functions, including secretion, absorption,motility, mechanical integrity, and mitosis. The cytoskeleton of highereukaryotic cells consists of three highly abundant major protein families.[1]

1. MICROFILAMENTS (MF)2.MICROTUBULES (MT)3.INTERMEDIATE FILAMENTS (IF)

MICROFILAMENTS

The actin cytoskeleton is highly conserved in all eukaryotic cells, and is composed of actin as its major component and actin-binding proteins (220). The human actin gene family includes three classes, named a-, b-, and g-actin. They modulate the function of the actin cytoskeleton in terms of polymerization and dynamics, cross-linking and bundling,nucleation and branching, actin-membrane interaction,cell-ECM interaction, cell-cell interaction, kinesis dynamics, contractility, scaffolding, and signaling[1].(Fig.1)

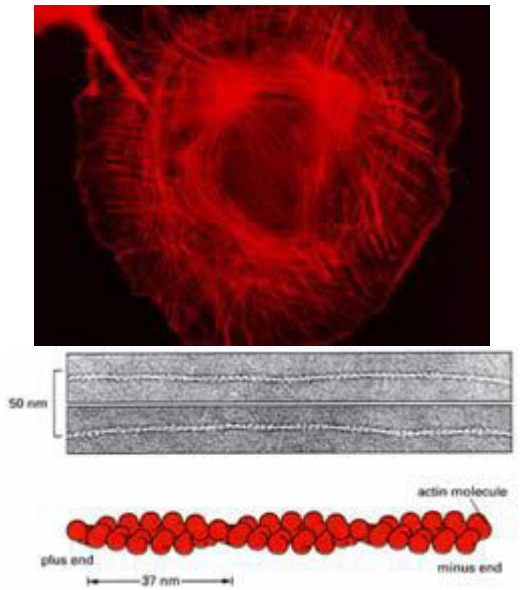
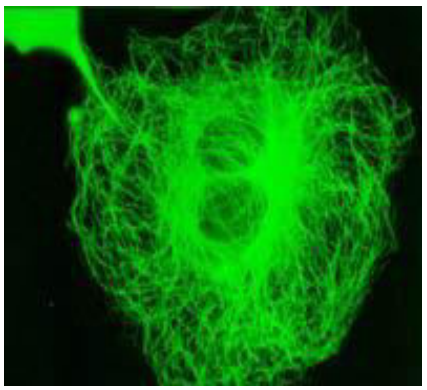


Figure 1: Structure of microfilament (The Cytoskeleton, 09/07, MER Boris Hinz, PhD, EPFL/SB/IPMC/LCB)

MICROTUBULES

Microtubules are composed of tubulin, which is found in all dividing eukaryotic cells and in most differentiated cell types MT are noncovalent polymers of tubulin and consist of heterodimersofAlpha- and beta-tubulin monomers, which are ,50% identical at the amino acid level. A third tubulin, gamma-tubulin, is expressed in animals, plants, fungi. A fourth tubulin, delta-tubulin, was described in *Chlamydomonas*, which functions in the maturation of basal bodies/centrioles.

It has structures such as flagella, cilia and lamellipodia and plays important roles in both intracellular transport (the movement of vesicles and organelles, for example) and cellular division.[1](Fig.2)



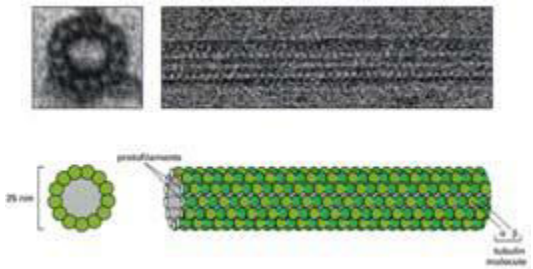


Figure 2: Structure of microtubule (The cytoskeleton, 09/07, MER Boris Hinz, PhD, EPFL/SB/IPMC/LCB)

INTERMEDIATE FILAMENTS

Intermediatefilaments are the third major cytoskeletal protein. They are divided into five types based on genomic structure and amino acid sequence homology. This excludes the ‘‘hard’’ keratins found in hair and other appendages, the lens proteins phakinin and filensin, and the neuroepithelial and muscle protein nestin . Type I–IV IF proteins are cytoplasmic and are expressed in a tissue-specific manner, whereas type V IF consist of the nuclear lamins. The type I and II keratins (also called ‘‘soft’’keratins or cytokeratins) are found specifically in epithelial cells, consist of at least 20 members (K1–K20) that are expressed in a cell type-specific manner, and form obligate noncovalent type I and II heteropolymers.

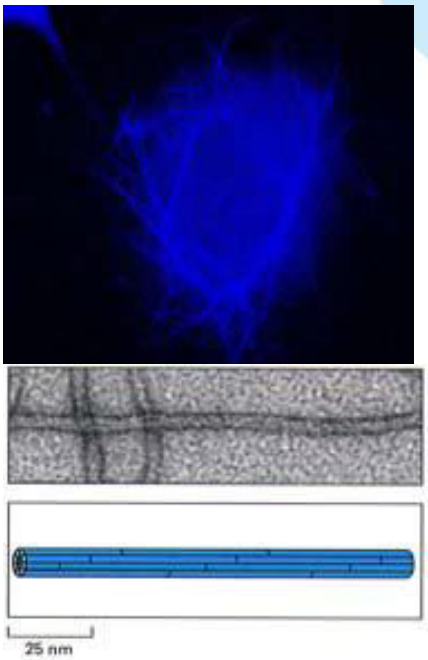


Figure 3: Structure of intermediate filament (The Cytoskeleton, 09/07, MER Boris Hinz, PhD, EPFL/SB/IPMC/LCB)

Other IF proteins include *TYPE III vimentin* of mesenchymal cells, *desmin*of muscle cells, *glialfibrillary* acidic protein of glial cells and *astrocytes, and peripherin* of peripheral neurons. *TYPE IV neuronal* IF include three neurofilament proteins (NF-L, NF-M, and NF-H) and a-internexin.[1] (Fig.3)

CYTOKERATINS OR KERATINS

Keratins (previously also called cytokeratins) are filament forming proteins of epithelial cells and are essential for normal tissue structure and function.[2]The Cytokeratins are the typical intermediate filament proteins of epithelia, showing an outstanding degree of molecular diversity. Heteropolymeric filaments are formed by pairing of type I acidic keratins as K9-20and type II basic keratins as K1-8 molecules. As part of the epithelial cytoskeleton, Cytokeratins are important for the mechanical stability and integrity of epithelial cells and tissues. Moreover, some Cytokeratins also have regulatory functions and are involved in intracellular signaling pathways, e.g. protection from stress, wound healing, and apoptosis.[3] Subsequent research of these structural proteins led to the classification of mammalian keratins into two distinct groups based on their structure,function and regulation. “Hard” keratins form ordered arrays of IFs embedded in a matrix of cysteine rich proteins and contribute to the tough structure of epidermal appendages. “Soft” keratins preferentially form loosely packed bundles of cytoplasmic IFs and endow mechanical resilience to epithelial cells.[4]

CLASSIFICATION OF CYTOKERATINS

I) Based on isoelectric point [5]
- Type I (isoelectric point below 5.5) (Ck 9 to Ck 20
- Type II (isoelectric point above 5.5)(Ck1 to Ck8

II) Based on Molecular Weight [6]
- Type I (40 – 65 kDa
- Type II (50 – 70 kDa

III) Based on pH [3]
- Type I (Acidic) (pH 4.5 – 6.0
- Type II (Basic) (pH 6.5 – 8.5.

IV) Based on X-ray Diffraction pattern [7]
- Alpha Keratin.
- Beta Keratin
- Feather Keratin
- Amorphous Keratin.

V) Based on Physical properties [7]
- Hard Keratin.
- Soft Keratin.

FUNCTIONS OF CYTOKERATIN

The cytokeratin cytoskeleton protects cells against mechanical stress through formation of a 3-D complex that associates with proteins of hemidesmosomes and desmosomes. Cytokeratin associations with the nuclear envelope probably play a nonstructural role. K8 and possibly other cytokeratins can protect tissue from injury by serving as a "sponge" for stress activated phosphate kinases. Evidence for this role has been obtained in hepatocytes isolated from mice synthesizing keratins that contain mutated phosphorylation sites including K8 and K18, which were mechanically stable following liver perfusion. Epithelial sheet migration is a fundamental process in both morphogenesis and tissue repair that requires maintenance of cell–cell junctions. Cytokeratins interact with desmosomes and hemidesmosomes, thus contributing to cell to cell adhesion and to connection with the underlying connective tissue.[3] A role in cell cycle regulation has been recognized. An increased nuclear accumulation of the regulatory protein has been detected in hepatocytes of K8 and K18 null mice. A significant number of these cells contain enlarged nuclei with a doubled DNA content; indicating that the absence of K8 or K18 disturbs cell cycle, drives cells into the G2-S phase and leads to aberrant cytokinesis. Mutation of distinct serine residues also causes a cytokinesis defect. Cytokeratins have been shown to attenuate apoptosis both at the death receptor and cell-intrinsic pathway levels.Intermediate filaments participate in targeting proteins to their proper subcellular compartments, by maintaining the polarity and the domain content in plasma membrane-associated proteins in polarized epithelia.[8]

STRUCTURE OF CYTOKERATIN

Cytokeratins share a homologous basic structure with all intermediate filament proteins. The central alpha – helical rod domain, composed of 310 – 315 amino acids, is responsible for dimerization and high order polymerization and is composed of four highly conserved domains 1A, 1B, 2A & 2B.The alpha helix consists of heptad amino acid repeats in which the first and the fourth residues are hydrophobic, residing close together on the surface of the helix and enabling two adjacent polypeptides to create a coiled coil. There is a stagger sequence in the helix 2B domain that is associated with reversal of direction of the alpha helix. Mutations that lead to shortening of rod domain yield keratins that are not only unable to assemble in to filaments but also interfere with the pre existing keratin filament network, since keratins are highly dynamic with reversible assembly and disassembly.[9]The four highly conserved domains are separated by non-helical linker domains, (L1, L12, L2). Since L1 and L12 are rich in both glycine and proline, they disrupt the alpha helix more effectively than glycine rich L2. Mutations in the keratin 5 and 14 are clustered in the L12 linker domain. These linker domain mutations disrupt the beta sheet structure of the L12 domain and prevent proper filament assembly between keratin 5 and 14. The amino terminal head and carboxy terminal tail regions, which confer antigenic specificity to individual keratins consists of two highly homologous subdomains (H), two variable subdomains (V), and two highly charged end subdomains (E) (Fig: 2). In hair keratins, these domains are cysteine rich, permitting the formation disulphide bonds that confer additional stability to their hair shaft.

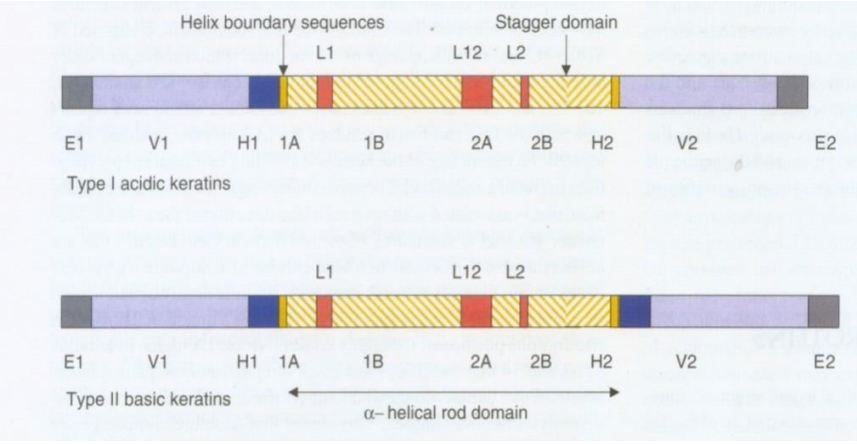


Figure 6: Structure of cytokeratin

The end regions of keratins are important for a variety of protein interactions. Mutations affecting the tail domain of keratin1 cause failure of keratin bundling, retraction of the cytoskeleton from the nucleus and failed translocation of loricrin to the desmosomal plaque.[10]

TYPES OF CYTOKERATIN

Different types of keratins are distinguished according to various characteristics, such as physicochemical properties,or according to the cells and tissues that produce certain keratins. Keratins in simple, non-stratified epithelia are ofdifferent types than those in stratified epithelia. Epithelial cells in simple as well as in stratified epithelia always synthesize particular keratins on a regular basis. These keratins are referred to as the primary keratins of epithelial cells, such as K8/K18 in simple epithelia or K5/K14 in stratified epithelia.These epithelial cells can also produce other keratins in addition to or instead of the primary keratins and these keratins are referred to as secondary keratins, such as K7/ K19 in simple epithelia or K15 and K6/K16 in stratified epithelia.

KERATIN K1[12]

The MW of K1 is variable among mammals. For example, in human epidermis K1 has a MW of 65 kDa**.** K1 and its partner K10 are produced in the suprabasal cells of the epidermis and are therefore regarded as important for post-mitotic differentiation in stratified keratinizing and cornifying epithelia.

KERATIN K2 (K2E)[12]

The MW of K2 is,65.5kDa in humans**.** K2 is a regular component of the epidermal cell cytoskeleton and is expressed most commonly in the suprabasal cells of the third or fourth layer of the *Stratum spinosum*. In mechanically stressed epithelia (e.g. ear,foot pad and tail of mouse), the synthesis of K2 is increased and induced by the underlying dermis.K2 can also be expressed in the superficial cells of the epithelium of the oral mucosa, which indicates an advanced orthokeratinization of those epithelial cells.

KERATIN K3:[12]

K3 has a MW of 63 kDa and an isoelectric pH of 7.5. The gene encoding K3 (*KRT3*) is active in humans, chimpanzees, dogs, cows and rabbits but not in mouse, guinea pig and pig. In the mouse at least,*KRT3*has become inactive and K3 is substituted by K4.

KERATIN K4[12]

K4 has a MW of 59 kDa and an isoelectric pH of 7.3. K4 and its partner K13 are produced in the differentiating suprabasal cells of the oral epithelium**.** Small amounts of K4 arealso produced in the cells of the transitional epithelium of the renal pelvis, ureter and urinary bladder.

KERATIN K5: [12]

K5 has a MW of 56 kDa and an isoelectric pH of 7.4. It is produced together with its partner K14 as the primary keratins of the basal cells in the stratified epidermis. Small amountsof K5 have also been detected in the cells of the transitional epithelium of the renal pelvis, ureter and bladder. K5 is produced in the mitotically active basal cells of stratified epithelia.

KERATIN K6:[12]

K6 has a MW of 56 kDa and an isoelectric pH of 7.8. K6 and its partners K16/K17 are expressed in a variety of internal stratified epithelia, such as those of the tongue, palate and female genitalia. Additionally, K6 is produced in the suprabasal cells of the palmar and plantar epidermis, of the nailand of the cells in the outer root sheath of the hair follicle. K6 is also produced in the hyper-proliferative epithelial cells of cancer and in wound healing. The expression of this keratin is upregulated in wound repair and in skin diseases.

KERATIN K7:[12]

K7 has a MW of 54 kDa and an isoelectric pH of 6.0. K7 is a secondary keratin of simple epithelia. It is also expressed in the cells of the renal tubule and the collecting duct of the kidney, as well as in the cells of the transitional epithelium of the mucosa of the renal pelvis, ureter and bladder. K7 is also expressed in theepithelial cells of the nail bed epidermis.

KERATIN K8:[12]

K8 has a MW of 52.5 kDa and an isoelectric pH of 6.1. In rats, its orthologue has a MW of 55 kDa and its pI is 6.4 .K8 forms heterodimers with the acidic K18 or K19 .K8 and its acidic partner K18 are considered primary keratins because they are the first to be produced in the simple epithelia of embryos . Inhuman fetal skin, the epithelial cells of the ectoderm and periderm express K8.

KERATIN K9[12]

In humans, K9 has a MW of 64 kDa and an isoelectric pH of 5.0. K9 is found in suprabasal cells

surrounding the intraepidermal portion of the ducts of sweat glands. The cross-reactivity of anti-human K9 antibody with bovine and equine tissues suggests that K9 of human, cow and horse have a similar epitope despite the considerable differences in their amino acid sequence and type. The amino acid sequence of K9 shows a remarkable similarity to that of K10 but also reveals striking differences in the subdomain 1A of the rod domain.

KERATIN K10: [12]

K10 has a MW of 56.5 kDa and an isoelectricpH of 5.3. It is the main type I keratinexpressed in the post-mitotic keratinizing cells in thesuprabasal layers of the epidermis and other cornifying stratified epithelia.The presence of K10 in a keratinocyte apparently prevents further cell divisions. The expression of K10 isdownregulated in injured epidermis. In differentiating suprabasalkeratinocytes of the epidermis,K10 is expressed prior to K9

KERATIN K11:[12]

K11 turned out to be a polymorphic variant of K10 due to changes in the tail domain of K10. Therefore, this label is no longer used to identify keratins.

KERATIN K12:[12]

K12 has a MW of 55 kDa and an isoelectric pH of 4.9; it is expressed only in the keratinizing suprabasal cells of the external stratified epithelium of the human cornea. Its partner for the formation of heterodimers is the basic K3. In the mouse and pig, the K3 gene is inactive and therefore K4 forms heterodimers with the acidic keratin K12.

KERATIN K13:[12]

K13 has a MW of 54 kDa and an isoelectric pH of 5.1. It is expressed in the cells of the transitional epithelium of the mucosa of the renal pelvis, ureter and urinary bladder. K13 isalso expressed in the suprabasal cells of the oral mucosa, esophagus and fore-stomach. K13 is the characteristicacidic keratin produced in the suprabasal cells of non-cornifiedstratified epithelia.[31]

KERATIN K14:

In humans, K14 has a MW of 50 kDa. Its isoelectric pH is 5.3. K14 appears to be a fundamental keratin of all keratinocytes in stratified epithelia. The expression of K14 (and of its partner K5) increases in embryonic epithelial cells, as these cells become basal cells of stratified epithelia. K14 is synthesized in the basal cells of the inter-follicular epidermis and upper part of the outer root sheath of hair follicles.

KERATIN K15:

In humans, K15 has a MW of 50 kDa and an isoelectric pH of 4.9. The synthesis of K15 may be upregulated in the absence of K14. K15 seems to be a secondary keratin in the basal keratinoblasts of theepidermis. The expression of K15 appears to be associated with a more mature type of basal cells that is more stable and has a lower rate of cell division. K15 is present in larger amounts in the basal cells of thin skin than, for example, in those of thethick plantar skin with its rapid turnover.

KERATIN K16:

K16 has a MW of 46 kDa and an isoelectric pH of 5.1. K16 expression defines a subset of epithelial cells during the morphogenesis of the skin and of cells in the companion layer of the outer root sheath of hairs. The expression of K16 does not coincide with the expression of its usual binding partner for heterodimerization, K6, during the embryonic development of the murine skin K16 marks cells that are presumably in an intermediate state of cell differentiation between basal and suprabasal cells, and it may provide sufficient structural stability by allowing the flexibility required for cell movement or mitosis.

KERATIN K17:[12]

K17 has a MW of 48 kDa in both humans and mice and an isoelectric pH of 5.1. K17 has been observed in small amounts in the cells of the simple epithelium of the seminal vesicular gland and epididymis, in basal cells of transitional and pseudostratified epithelia, in myoepithelial cells of secretory units of exocrine serous glands, and in injured human interfollicular epidermis. In the interfollicular epidermis, K17 is expressed in the suprabasal cells only when the epidermis is injured.

KERATIN K18: [12]

In humans, K18 has a MW of 44 kDa and an isoelectric pH of 5.5. In the rat, K18 has a MW of 49 kDa and an isoelectric pH of 5.38. The epithelial cells of the ectoderm and periderm of the human fetal skin express K18 . K18 is also expressed in most of the simple epithelia of the human male urogenital tract. K18 is a constituent of the cytoskeleton in the cells of simple epithelia, such as the hepatocytes, the cells lining the bile duct and renal tubules, and the cells of the intestinal, bronchial and alveolar epithelia.

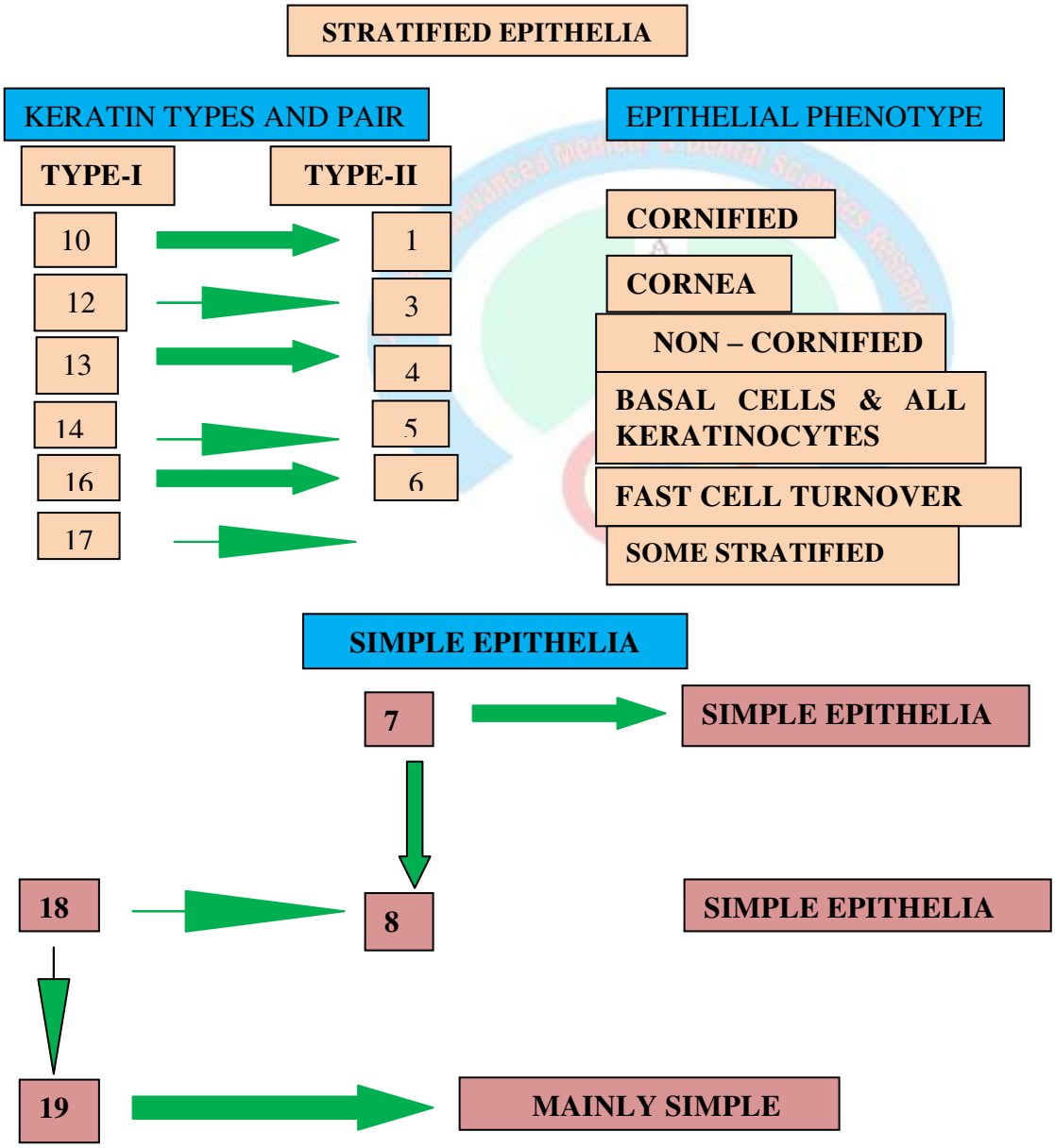
KERATIN K19:[12]

K19 has a MW of 40 kDa and an isoelectic pH of 5.2. The amino acid sequences of human K19 and of thecorresponding bovine orthologue are 89% identical. K19 is the smallest keratin because it is lackingthe typical tail domain. K19 is the only'simple' keratin produced in the cells of stratified epithelia. K19 is rapidly inducible in a variety ofepithelia, such as human epidermal keratinocytes andconjunctival epithelial cells. K19 can formintermediate filaments with K8 but it can also partner with K5 and K7. K19 is alsoexpressed in the basal layer and periderm of the skin in ahuman fetus.

KERATIN K20:

K20 has a MW of 48.5 kDa. Its amino acid sequence is quite different from all other type I keratins. K20 has been found in epithelial cells of the murine lung and rat placenta. K20 is produced in the epithelial cells of the gastric mucosa. K20 is also expressed in the epithelium of the intestinal mucosa and of the uterus and urinary bladder. The cells of the intestinal epithelium produce K20 in addition to K18. K20 is also expressed in Merkel cells. In the developing oral mucosa, K20 is exclusively specific to taste bud anlagen and bipolar cells.

PAIRING OF CYTOKERATINS



ANTIBODIES TO CYTOKERATINS

In the early days of immunohistochemistry, most antikeratin antibodies used in surgical pathology were not reactive to a specific keratin; rather they were mixed monoclonal antibodies or polyclonal antibodies that reacted to several keratins. Currently, high quality anti-keratin monoclonal antibodies to all of the 20 keratins are commercially available.[13,14]
The commonly used antibodies are:

Pankeratin cocktail

The cocktail antibodies contain monoclonal antibodies to AE1, AE3, CAM5.2 and 35BH11. It reacts to all epithelial tissues and their tumors.

Clone LP34 antibody

This is a broad-spectrum monoclonal antibody that is reactive to K5. K6, K8, K17 & K19. It is positive on both simple glandular and stratified squamous epithelium. LP3 can be used as a pancytokeratin antibody to differentiate carcinoma from sarcoma, lymphoma or malignant melanoma.

Pancytokeratin antibodies

This contains monoclonal antibodies to K5, K6, K8& K18. They recognize all epithelial tissues and their neoplasms.

Wide spectrum screening antibody

This is a rabbit anti-cow polyclonal antibody that also reacts with human keratins.

AE1 & AE3 antibody

This antibody is a mixture of AE1 clone and AE3 clone. Monoclonal AE1 recognizes type I keratin, while AE3 recognizes type II keratins. Thus, AE1 and AE3 is a pan-specific antibodies for human keratins.

High molecular weight keratin antibody clone 34BE12

This antibody recognizes K1, K5, K10, and K14, which are expressed in complex epithelia, basal cells and myothelial cells.

CAM5.2

This antibody reacts with K8 and K18. In normal tissue, it stains simple and glandular epithelium. CAM5.2 stains most of the epithelial-derived tissues and their tumors. It is useful for the differentiation of adenocarcinoma from squamous cell carcinoma.

Anti-cytokeratin 5/6

This antibody reacts with K5 and K6, but does not react to K1, K7, K8, K10, K13, K14, K18 and K19. This antibody recognizes basal cells. A part of stratum spinosum of epidermis and mesothelium, but is not reactive with simple epithelium or their tumors.

SUMMARY AND CONCLUSION

There are several levels at which an understanding of intermediate filament expression has spread into the diagnostic field. The most widely used application has been to help clarify the tissue of origin in anaplastic tumors where diagnosis is based solely on histological criteria, which can lead to error and inappropriate treatment.

Some intermediate filament classes are sufficiently conserved in anaplasia to play a role as tissue – specific markers (e.g. keratin, desmin) although vimentin is too widely expressed to be diagnostically useful for many neoplasms and may also be co-expressed with keratins in high-grade carcinomas. Some antibodies to intermediate filaments now have a place amongst the most commonly used antibodies in diagnostic immunocytochemistry.

The keratins by showing a complexity of expression, which is tightly linked to differentiation, constitute important biological markers. The proteins are stable, relatively resistant to degradation, show great fidelity of expression and are very antigenic.

Keratins may serve as markers of early alterations indicative of premalignant and malignant lesions. But pathologists should be aware of the existence of some rare neoplasms, which in spite of their mesenchymal origin may show positivity for cytokeratins. The expression of cytokeratins in sarcoma is generally but not always accompanied by evidence of epithelial differentiation at light and electron microscopic level e.g. synovial sarcoma. Synovial sarcoma due to their monophasic and biphasic nature shows extensive keratin positivity with simple epithelial keratins (ck7, ck8, ck18, ck19 & ck20) as well as stratified epithelial keratins (ck5/6, ck10, ck13 & ck14).

The simple epithelium keratins that are not only associated with poorly differentiated squamous cell carcinoma but also with well differentiated tumors, its significance to prognosis now need to be assessed. Although reliable immunohistochemical methods do not yet exist to permit accurate differentiation of neoplastic lesions, these techniques are extremely powerful in the case of established neoplastic disease and such methods should become routine in all diagnostic histopathology laboratories.

Better understanding of cytokeratin pattern shifts during epithelial cell transformation and tumor

progression may be expected when the molecular regulatory mechanisms of the expression of cytokeratin have been explored. More precise localization of the different keratin species in the oral epithelia would be possible by correlation of biochemical characterization and immunohistochemical staining with monoclonal antibodies. Thus, complete reliance on keratins, as markers of histogenesis in malignant neoplasms should not be encouraged.

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