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"KERATINS IN GINGIVAL: A REVIEW"

Dental Science

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ABSTRACT

The epithelium of gingiva is of stratified squamous type. Keratins are proteins present in the epithelium which protect the gingiva against mechanical stresses. Keratins are classified into two types- type I (acidic) and type II (basic). This review focuses on the types, structure, and distribution of keratins in the gingiva. A brief note has also been added on the disorders of keratin-associated with oral mucosa.

KEYWORDS

Gingival Epithelium, Keratinization, Keratins, Keratinization Disorder.

INTRODUCTION

The gingiva is constantly under a wide variety of functional stresses. Thus, this need is met by the formation of intracytoplasmic filamentous arrays called keratins [1]. Keratins are defined as intermediate filament-forming proteins, (10 nm in diameter) with specific physicochemical properties, produced in any vertebrate epithelia. They form the cytoskeletal structural proteins of stratified keratinizing epithelia.[1] As a part of the epithelial cytoskeleton, keratins are important for mechanical stability of epithelial cells. In addition to providing stress-bearing functions, they also help in maintaining the cell shape.

Keratinization in Gingival Epithelium

The gingival epithelium consists of a continuous lining of stratified squamous epithelium. The main function of gingival epithelium is to protect the deep structures while allowing for a selective change with the oral environment. This is achieved via the proliferation and differentiation of keratinocytes. Keratinocytes are the chief cells of gingival epithelium. It receives its name because it can synthesize keratin.[2] In accordance to meet the functional demands, gingival demonstrates two types of epithelia first being keratinized epithelia like attached and free gingiva and the second one is nonkeratinised epithelia like sulcular and junctional epithelia.[1] Keratins that forms intermediate filament network which is responsible for maintaining the structural integrity of keratinocytes are the formed from a wide variety of proteins.[6]

Oral epithelia demonstrate one of the 2 patterns of epithelial maturation:

1. Keratinization—maturation of mucosa takes place through the formation of a surface layer of keratin.

A) Orthokeratinization—in this type of epithelial maturation absence of nuclei noted in the surface layer of squamous on maturation.
B) Parakeratinization—refers to the retention of pyknotic nuclei in the surface layer of squamous on maturation.

2. Nonkeratinization—refers to maturation without the presence of keratin layer. Hence nuclei retained in surface cells can be noted along with sparse keratin filaments in the cytoplasm.[1]

Structure of Keratin

Keratins are obligate heterodimer proteins, expressed in pairs of types I and II proteins. [1] The keratin proteins are composed of different polypeptide subunits characterized by their isoelectric points and molecular weights. [2] The molecular weight of human keratins ranges from ~44 to ~66 kDa.[3]

Each keratin is having a specific chain of amino acids as the primary structure of the keratin protein, which may vary in the number and sequence of amino acids, as well as in polarity, charge and size. [4] The amino acid sequence of specific keratin determines the molecular structure and properties of the secondary, tertiary and quaternary structures of keratins, and also the as the nature of the bonds (e.g. covalent or ionic) to other components of the cytoskeleton amino acids as the primary structure of the keratin protein, which may vary in the number and sequence of amino acids, as well as in polarity, charge and size.[4]

The amino acid sequence is somewhat larger than the sequence of matured keratin, which indicates a post-translational modification of the keratin preceding the formation of the keratin filaments. Post-translational modifications of keratins, such as the formation of disulfide bonds, phosphorylation, glycosylation, deimination or inter- and intrachain peptide bonds, can influence the conformation of the molecule and the formation of keratin filaments.[4]

Function of Keratin

Keratin provides mechanical support, helps in the maintenance of cellular architecture. It participates in intracellular transport, intercellular junction formation and wound healing. It regulates protein synthesis and cell growth. It protects from stress, apoptosis and variations in hydrostatic pressure.[1]

Classification of Keratin Proteins

Keratin proteins are divided into two families based on amino acid sequence and charge:

A) Type I family of acidic proteins (keratins K9- K20)
B) Type 11 family of basic or neutral proteins (keratins KIK8).[5]

In any given epithelial cell type, at least two keratin proteins (one type I and one type II) are co-expressed; these proteins assemble into heteropolymers and form the 10-nm keratin IFs that are part of the cytoskeleton in virtually all epithelial cells.[5]

A) Type I includes K9-K10, K12-K28, K31-K40[1]
B) Type II includes KI-K8, K71-K86[1]

An orthokeratinized area expresses with high intensity of keratin K1, K2, K10 through K12 which are specific to epidermal differentiation type and with less intensity in parakeratinized areas. Highly proliferative epithelium expresses K6 and K16, and K5 and K14, which are stratification specific cytokeratins, are also present. K19 expressed in parakeratinized, which is usually absent from orthokeratinized normal epithelia.[3]

Cytokeratins

Cytokeratins form the cytoskeleton of all epithelial cells, along with microfilaments and microfibrils. Cytokeratins are seen not only within the cells but also in cell contact areas like desmosomes. [7] Distribution of cytokeratins is highly specific and it may vary with the site, type of epithelium and extent of differentiation. Cytokeratins demonstrate specific expression pattern which is site-specific and varies with the level of differentiation. This property of cytokeratins has evolved as a potential epithelial differentiation marker in cell biology, embryology and surgical pathology. Cytokeratins are the 'gold standard markers' in immunohistochemical diagnosis, classification and subtyping of carcinomas and detection of unclear metastasis. [1]

Keratin Polypeptides of Gingiva

As with other non keratinized epithelia, the sulcular epithelium lacks granulose and corneum strata and K1, K2 and K10 through K12 cytokeratins, but it contains K4 and K13, the so-called "oesophagal-type cytokeratins". It also expresses K19 and normally does not contain Merkel cells.[3]The different keratin polypeptides of the junctional epithelium have a particular histochemical pattern. Junctional epithelium expresses K19, which is absent from keratinized epithelia, and the stratification specific cytokeratins K5 and K14. [3]Another particular behaviour of the junctional epithelium is the lack

of expression of K6 and K16, which is usually linked to highly proliferative epithelia, although the turnover of cells is very high.[3]

Keratin Expression in Gingival Epithelium- The following table shows the keratin expression in the gingival epithelium (Table-1).[6]

Table- 1: showing keratin and its distribution gingival epithelium.

Keratin	location
K5/14	Basal cell layer
K19	Basal cell layer of junctional epithelium and gingival margin
K8,18,13,16,19	Superficial layers of junctional epithelium
K4, 13,16	Superficial layer of gingival margin
K1/10, K6/16 and K2p	Superficial layers of outer gingival epithelium

A. Keratin Disorders with Gingival Involvement

Disorders in keratin may be genetic or acquired. Since the discovery of the first genetic disorder of keratin, Epidermolysis Bullosa simplex (EBS), numerous keratin mutations are being identified as the cause of several skin and mucosal disorders. Also, abnormal keratinization is part of several acquired oral diseases.[1]

1. **Epidermolysis Bullosa Simplex**
   Mutations in keratin genes have been found to cause several dominantly inherited skin diseases, including Epidermolysis Bullosa (EB) simplex (involving mutations in K5 and K14), epidermolytic hyperkeratosis (mutations in KI and K10).[5]
   Oral manifestations: Mucosal involvement uncommon; mild involvement- gingival erythematic, tenderness, recession and reduction in the depth of buccal vestibule.[3]
2. **Pachyonychia Congenital**
   Pachyonychia congenital is the name given to another group of autosomal-dominant epithelial disorders that exhibit various ectodermal abnormalities, including hypertrophic nail dystrophy and non-epidermolytic PPK (thickening of palms and soles). In the more common ladassohn-Lewandowsky form, there is also oral leukokeratosis (leukoplakia) very similar to that seen in white sponge nevus, while in the Jackson-Lawler type there is no oral leukokeratosis, but teeth that are often malformed are present at birth, and patients have cutaneous cysts.[5]
   Oral Manifestations: Hyperkeratosis of the oral mucosa.[3]

B. Keratin Disorders with Oral Mucosa Involvement

1. **White sponge nevus (Canon's disease)**
   It is a benign autosomal-dominant disorder which affects non-keratinizing stratified epithelia including the oral cavity and, to a lesser extent, the oesophagus and anogenital mucosa. Typically, it is characterized by white spongy plaques in the mouth (oral leukokeratosis) with acanthosis and perinuclear aggregation of keratin filaments in suprabasal cells.[5]
2. **Dyskeratosis congenital**
   Leukoplakic lesions on the tongue, buccal mucosa- one third become malignant.[3]
3. **Hereditary benign intraepithelial Dyskeratosis**
   Thick corrugated white plaques on buccal and labial mucosa[3]
4. **Darier's disease**
   Asymptomatic multiple, white, flat-topped papules on the hard palate and alveolar mucosa may fuse to give a cobblestone mucosal appearance.[3]

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