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Chapter

Contribution of Environmental Constituents in the Genomic Disruption of Cytokeratins

Vishnu Sharma, Tarun Kr. Kumawat, Garima Sharma, Rashi Garg and Manish Biyani

Abstract

Cytokeratins are keratinous protein and assist cells to reduce mechanical stress on the intracytoplasmic layer of epithelial tissue. There are several unspecified mutations in the epithelial layer that may induces by environmental mutagens and pathogens. The unspecified mutations in the epithelium surface also disrupt biology of skin at multiple different levels and cause innate keratinizing disorders. These serve as a root generator of neurohormones and neuropeptides which mainly partake in the disruption. Generally, all 54 unique genes of human keratin partake in mutations and cause cutaneous tissue fragility, skin hypertrophic, and malignant transformation. In this chapter, unspecific factors that involved in the pathogenesis of skin diseases and the ways by which such keratin changes might harness to alleviate different skin conditions are also included. Consequently, the contribution of environmental changes in the frontier of mutations or misregulations of the cytokeratin genes, is also cited here.

Keywords: keratins, skin barrier, keratinopathies, keratinocytes, protease allergens

1. Introduction

Cytokeratin is an intermediate keratinous protein found in the intracytoplasmic cytoskeleton of epithelial tissue. Cytokeratin possess essential components for the epithelium layer with diameters of 6 nm (microfilaments) to 25 nm (microtubules). The microfilaments or microtubules support cells to resist mechanical stress [1–3]. In the 1970s, the term 'cytokeratin' was derived through the protein characterization in the intermediate filament [4]. Later, in 2006, with the new systemic nomenclature, the terminology "cytokeratin" was termed as keratins. This nomenclature was under the nomenclature of the Human Genome Organization (HUGO) for both the gene and protein names [5, 6].

Keratin are the most complex protein in vertebrates and in filamentous form are essential epithelial cell structural stabilizers. That's why; keratin is of unprecedented importance in genetics, embryology, pathology, and dermatology [7]. Keratin filaments are usually integrated with desmosomes and hemidesmosomes. They contribute: to the cohesion of the epithelial cells; for attachment of the basement membrane; and for epithelial connectivity tissue transition [8, 9]. Although few keratin structures/skeletons also found as scattered or dispersed between

keratinous filaments in the cytoplasm of the internal parenchymatous organs. This behavior contributes to the (simple) unstratified epithelial membrane. These component sprouts increase as tonofilaments and transformed into a cornified stratified epithelial sheet [10].

Although, Keratin are classified into alpha and beta keratins according to the amount of sulfur content and structure [11]. Alpha (α) keratin form epithelial layers in all vertebrates [12, 13]. Configurationally, alpha (α) keratin has abundant amounts of the hydrophobic amino acids: methionine, phenylalanine, valine, isoleucine, and alanine. Due to the occurrence of these amino acids, alpha (α) keratin is extraordinary for its strength, elasticity, tiredness, insolubility, and durability [14]. Apart from the diversity of the epithelial keratins ('soft' or 'cyto'); hair and nails are built from a very distinct subfamily of 'hard' or 'trichocytic keratins' [10, 15–18]. Since they are enriched in stacked β pleated sheets and are known as corneous beta-protein" or "keratin-associated beta-protein [19–20]. The epithelial keratins differ in their non-α-helical head and tail domain. This is due to the existence of high sulfur contents which is primarily responsible for the high filament linkage level of the keratin-associated protein [21, 22].

In filamentous form, keratin possesses a head-rod-tail structural arrangement with its basic polypeptide configuration consisting of a core alpha-helical coiled rod structure of about 310 amino acids in size. This central rod segment contains four helical structures interrupted by three short non-helical flexible reticulation/ Linker regions [9, 12, 23]. These linker or reticulation regions flank by the complex, non-helical amino-terminal head and carboxy-terminal tail domains. In the rod domain, a heptad repeat of amino acid residues is present. Furthermore, near the middle of the domain, the "stutter" region is found and is a highly conserved segment among IFs. This area does not take part in the development of coiled-coil heterodimers but plays specific roles in the extension and rotation characteristics of keratins [24, 25]. At the beginning and end of the heptad repeat regions in the rod domain; are the highly conserved helix initiation motif (HIP) and helix termination peptides (HTP). Respectively, HIP & HTP, both consist of 20 amino acid sequences related to different keratin gene families [26–28]. The heteropolymeric structure of type I and type II keratin collectively generate a filamentous form. These are all aligned laterally with a scalable and parallel overlap and form KIFs through lateral stacking and polymerization of chains [9, 29, 30].

In cytokeratins, all of the intermediate filament proteins have the template/ prototype structure that contains a central coiled-coil helix (310–350 amino acids). These are surrounded by the variable-length globular NH2-terminal head and COOH end-end tail domains [31–33]. Here, the keratin type I chain form a paired dimer with its type II counterpart and build an antiparallel fashion to a tetramer. Two tetramers transversely bind and resulted in a protofilament. Then, protofilaments are twisted into a keratin filament rope. Therefore, each keratin filament has a cross-section of 32 individual helical coils (**Figure 1**) [34–38]. The globular end-domains in most of the intermediate filament proteins contain all known sites for phosphorylation, glycosylation, and other relative activities [33, 39–42].

Usually, cytokeratin has an outstanding standard due to its high molecular diversity. The molecular weight of human keratins ranges from 44 to 66 kDa. In human, all 54 distinct functional keratin genes are found on chromosomes 12 & 17 and represent the typical intermediate filament category of epithelial cells. All keratin filaments are specifically bundled as tonofilaments in some but not all endothelium [43, 44]. In humans, all 54 distinct functional keratin genes are characterized as keratin type- I genes (17 epithelial and 11 hair keratin genes) and keratin type- II genes (20 epithelial keratins and 6 hair keratins) (**Figure 2**) [45, 46]. Type I
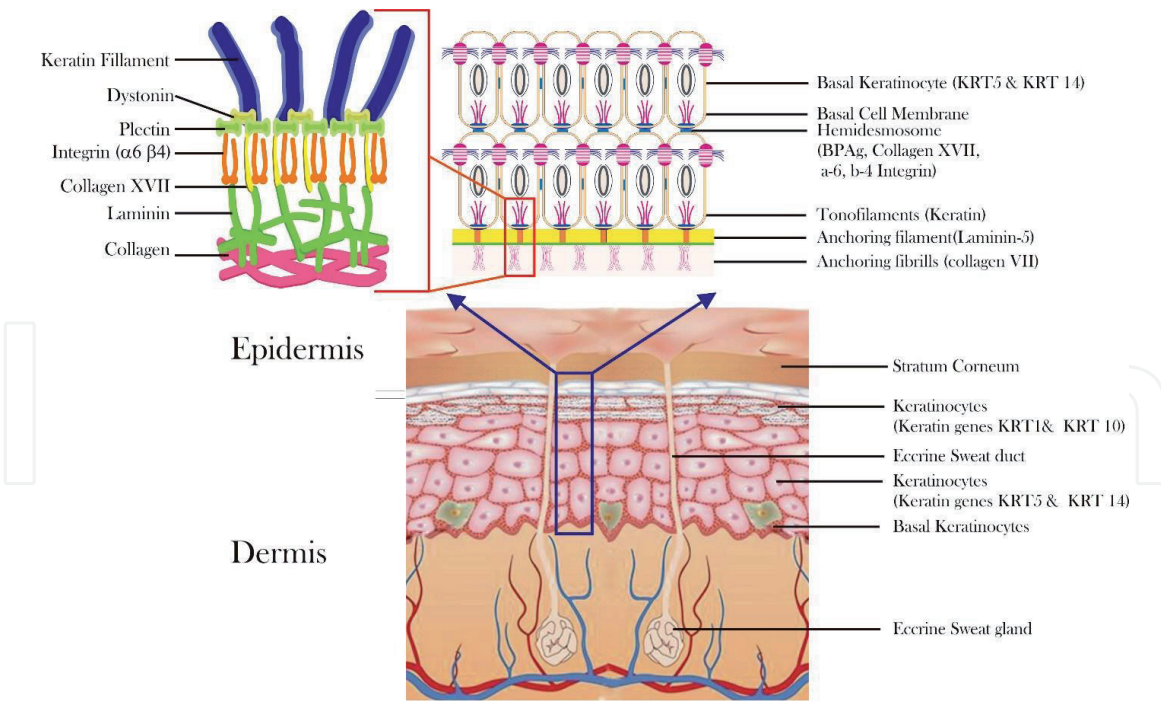
Figure 1.
Differentiated Keratinocytes in Structure of Human Skin.
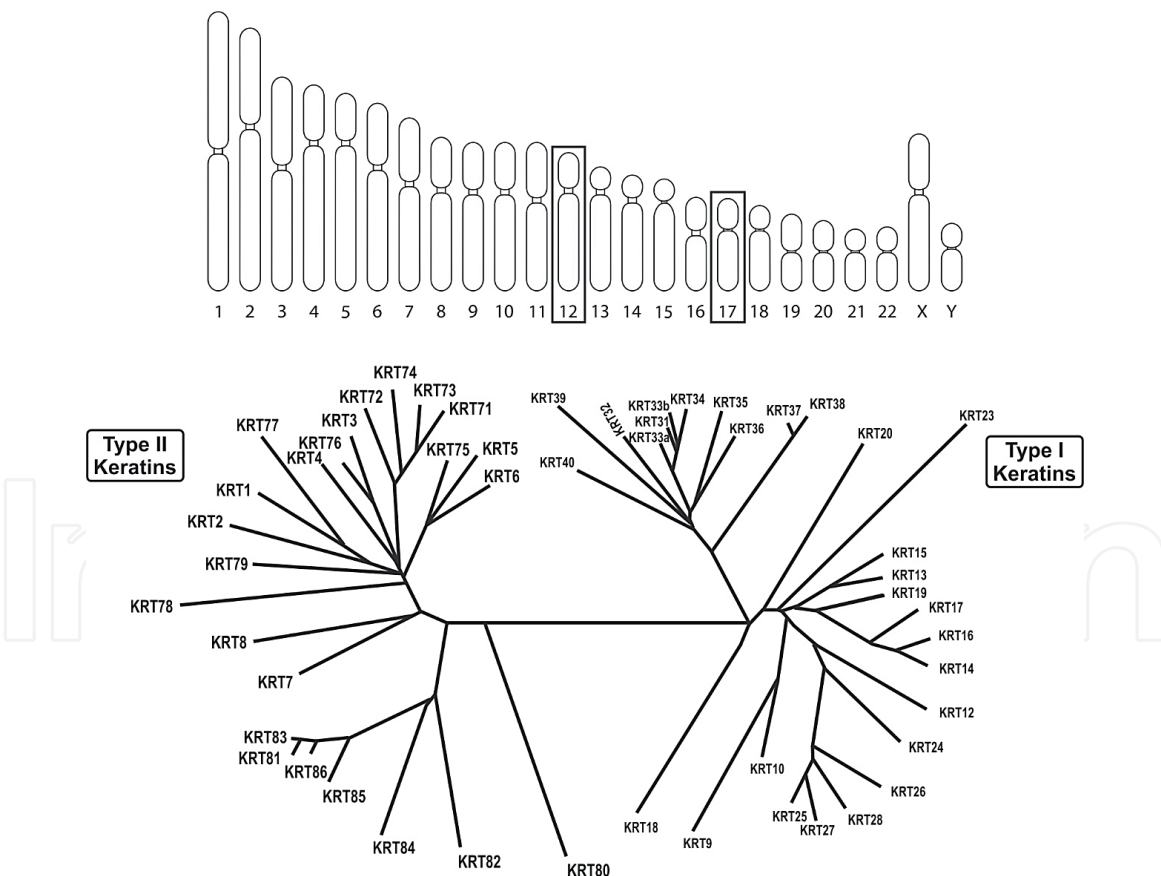

Figure 2.
Ideogram and Phylogenetic description of Mammalian Keratin Chromosome (i.e. 12 & 17).

keratin comprises the KRT9–KRT10, KRT12–KRT28, and KRT31–KRT40 (including KRT33a and KRT33b) genes, while type II keratin has KRT1–KRT8 (including KRT6a, KRT6b, and KRT6c) and KRT71–KRT86. Besides, the "stratified keratins" comprise KRT1 to KRT6 and KRT10 to KRT17 [10, 47–51].

The human skin is the largest of the epithelial layers of the body and has a crucial strategic defensive position at the boundary between the interior and exterior environment of the body. Histologically, the skin is made of multi-layered, non-vascular, stratified epidermal squamous tissues which are extending to dense fibrous connective dermal tissues [52, 53]. For each cytoskeleton of the epithelial layer, there are three abundant filament systems available: actin-microfilament systems (MFs; 7–10 nm diameter; IFs; 10–12 nm diameter), interlinked microtubules, and (MTs; diameter 25 nm). Each filament system comprises a corresponding gene family with specially regulated cell-tissue regulators that encode each protein family [54]. Mutations in any cutaneous-associated keratin genes are increasingly apparent, which causes a host of hereditary skin disorders; and specified to weakened cell tissue integrity & damaged the skin [42, 55–57].

The regional specificity of keratin expression may add to the intrinsic specialization of regional keratinocyte stem cells. Disorders in keratin may be genetic or acquired. Several keratin mutations have been identified as a cause for many diseases in the skin and mucosal tissues [26, 58–60]. Beyond the biological roles, keratin expression describes cells not only as "epithelial," but as distinctive even for characterize stages of cellular epithelial differentiation from embryonic to adult or internal maturation programs throughout growth. [10, 61, 62].

Mutations in the keratin amino acid sequence significantly affect the montage of keratin filaments [63–65]. Keratin genes repeat along with frameshift mutation and generate the pseudogenes. Approximately 87% of individuals' keratin pseudogenes are equivalent to keratin genes 8 & 18 [66]. keratin pseudogenes continuously exchange their position on multiple chromosomes through crossing-overs or translocations [45, 67]. Mutations of keratin genes contribute to several human and murine skin disorders [68].

Keratinous genetic mutations cause various keratin disorders known as "Keratinopathies". In the last decades, the spectrum of skin disorders has been increased enormously due to the abnormal function of structural proteins (keratins, filaggrin, loricrin, cornified cell envelope, etc.) [26, 47, 69–73]. It has also boost up or affected by deficient enzymes or transport proteins that are essential for lipid metabolism in the epidermis (cholesterol sulphatase, lipoxygenases, ABCA12, etc.). Mutations in epidermal keratins cause several skin diseases like congenital ichthyosis, epidermolytic ichthyosis, congenital bullous disease, corneal dystrophy, erythroderma, and pachyonychia congenital [74–76]. All the above diseases are due to mutation in the corneal keratin genes (KRT3, KRT12); mutation in simple epithelial keratin genes (KRT8/18, KRT19, KRT9); mutations in epithelial keratin genes (KRT6A, KRT6B, KRT6C, KRT16 or KRT17); mutations inKRT1 or KRT10 or basal layer keratinocytes genes (KRT5&KRT14) [77, 78].

In the epidermis and associated skin appendages, mutagenic cutaneous disorders are commonly termed as genodermatoses [79]. Keratin mutations represent keratin-related disorders including epidermolysis Bullosa Simplex (Keratin gene 5& 14), Keratinopathic Ichthyosis (Keratin gene l, 2 &10), Palmoplantar Keratoderma (Keratin gene 9), Pachyonychia Congenital (Keratin gene 6a,6b1,16 &17), and Monilethrix (Keratin gene 81, 83 & 86), etc. [18, 26, 80–82].

Epidermolysis bullosa is one of hereditary keratin disorder specified as mechanic-blistered skin. Epidermolysis bullosa is caused by desmoplakin or plakophilin type mutations in keratin genes KRT5 and KRT14 [83, 84]. In the manifestation of Epidermolysis bullosa, skin fragility reveals and can be increased in fluid-filled blister form or by the erosion of the skin. It causes failure in keratinization and affects the integrity or the ability of the skin to resist mechanical

stresses. Hence, disease signs may extend for esophageal contraction, squamous carcinoma [85].

Epidermolysis Bullosa possess four main types: Epidermolysis Bullosa Simplex (EBS), Dystrophic Epidermolysis Bullosa (DEB), Junctional Epidermolysis Bullosa (JEB), and Kindler Syndrome (KS). In Epidermolysis Bullosa, all above disorders are inherited keratin disorder caused by mutations in Keratin genes 5 & 14 and plectin [86, 87]. The mutations in the gene of plectin are associated with muscular dystrophy. Symptomatically, Suprabasal epidermolysis causes fragility and blistering of skin or erosion by minor injury or friction (Rubbing or Scratching). Blistering may extend to mucous of the mouth with digestive tract and directly can affect the digestive system. Because of this, many infected children are poorly nourished and grow variably. The extended blistering cause irregular red patches of granulation sheath and rise to bleed regularly. In the enlargement of the disease, newborns lose essential metabolic nutriment and fluids. Consequently, granular sheath affects the respiratory tract and difficult to speaking and breathing [88, 89]. Besides, Kindler syndrome is a type of epidermolysis bullosa and causes skin blistering but often on the hands and feet. It generates scarring on the skin between the fingers and between the toes. Kindler syndrome is genetic dermatitis even though may also cause by ultraviolet (UV) rays and sunburn undoubtedly. The Kindler syndrome can expand on the outward of the oral cavity, throat, intestines, genitals, and urinary regions. Ultimately, the condition might be converted into squamous follicle melanoma [90–93].

Keratinopathic ichthyosis is a generative disorder in the human that occurs by a mutation in Keratin genes (KRT1, KRT2, and KRT10). It exhibits anomalies in the membranous filaments and develops the spectrum of clinical manifestations [26, 94, 95]. Therefore, it is also known as superficial keratin keratodermas [60, 96]. This disorder manifests symptoms as scratched skin fragility, blister generation over flexural areas on erythroderma, and thick stratum corneum. The blistering and erythema in Neonates appear by birth though over time manifestation increases. Usually, Palmoplantar keratoderma also appears with Keratinopathic ichthyosis. It exhibits the thickening of the palm's skin of the hands and soles of the feet [26, 97, 98].

Monilethrix is a pervasive innate disorder. It occurs due to mutation in the human keratin gene KRT86 and KRT81 [99–100]. Clinically, Monilethrix is distinguished by dystrophic hair reduced region or with complete alopecia. Hair shaft deformation is defined by elliptical nodes that are commonly separated by reductions in skin color, by the appearance of scars, scratches, or rashes at the constricted regions [101, 102]. Infected hair also exhibits scarcities in the cortex of the skeletal hair shaft proteins, especially for trichocyte keratins. Rarely, hair possesses regrowth through adolescence or pregnancy [103, 104].

Pseudofolliculitis Barbae (PFB) and loose anagen hair syndrome (LAHS) are other hair disorders due to mutation in the keratin gene KRT75. Certain gene is located in the form of a cluster on the long arm of chromosome twelve. It originates with the follicular infection on the neck and beard region of the face [105–108]. Sometimes disease also expands due to shaving on surrounding ingrown facial hairs, on the body wherever hair is shaved or plucked, including axilla, pubic area, and legs [18]. Apart from the cutaneous layer, nail dysplasias (Pachyonychia congenital) also take place in the hypertrophic portion of nails. It occurs due to mutation in the genes KRT6a, KRT16, and KRT107 [109, 110].

Ectodermal dysplasia is a separate one disorder similar to keratoderma or ichthyosis. It is associated with skin appendages bearing with the hair, nails, and sweat glands. Normally, this disorder is caused by a mutation in the KRT85 gene [111, 112].

2. Contribution of environmental constituents in mutation

Throughout the world, skin melanoma is the 19th most widespread cancer. Usually, almost all types of skin cancers are related to environmental factors including contact with immense ultraviolet radiation or due to sun exposure. Environmental mutagens may be synthetic or natural agents in nature [74, 113–116]. these mutagens produce genetic mutations or expand mutational activities during the life span [117, 118]. Most of the environmental mutagens possess genotoxic effects on the next generation via germ cells and continue in the inherent form.

Besides ultraviolet radiation, other radioactive, heavy metals, organic solvents or chemicals, viruses, bacteria, etc. also perform a role to cause cell damage [119–122]. Even, consumption of cigarette smoke, dietary contaminants including mycotoxin, aflatoxin B1, fat consumption, and unorganized stress are themselves integral environmental factors that contribute to cytokeratin disruptions [123]. All these agents are come in contact with the human through directly via skin & lungs or by ingestion. From this channel, these circulate in the body (blood, lymph glands, muscles, bones, tissues, and organs) and initiate mutations. In mutagenesis, these all mutagens penetrate directly to cellular and nuclear membranes and damage DNA by cross-linking (chemically gluing) two bases together. Sometimes, Mutagenesis is also caused by aberrant DNA methylation (epigenetic change) at the genomic level and post-translational modifications at the protein level. Finally, this results in genetic deficiencies cause.

3. Conclusion

Cytokeratins are essential protectors of epithelial structure found in the intracytoplasmic cytoskeleton of epithelial tissue. The occurrence of mutation in cytokeratin genes generates several genetic dermal disorders. In this genetic alteration, several environmental factors (ultraviolet, reactive oxygen species (ROS), deaminating agents, polycyclic aromatic hydrocarbon (PAH), ethylnitrosourea, azide, dyes, and heavy metals) take place as mutagen factors. The present chapter conclusively stated different cytokeratins disorders caused by environmental mutagens, i.e., synthetic or natural mutagens. In the end, based on environmental mutagens contributions, it can be stated that the genetic and epigenetic effects, arise/enhance through environmental mutagens/carcinogens, are the subject of innovative research.

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