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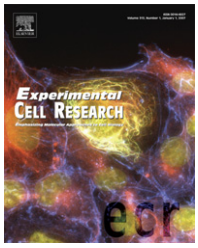

Review Article

Diseases of epidermal keratins and their linker proteins

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ABSTRACT

Epidermal keratins, a diverse group of structural proteins, form intermediate filament networks responsible for the structural integrity of keratinocytes. The networks extend from the nucleus of the epidermal cells to the plasma membrane where the keratins attach to linker proteins which are part of desmosomal and hemidesmosomal attachment complexes. The expression of specific keratin genes is regulated by differentiation of the epidermal cells within the stratifying squamous epithelium. Progress in molecular characterization of the epidermal keratins and their linker proteins has formed the basis to identify mutations which are associated with distinct cutaneous manifestations in patients with genodermatoses. The precise phenotype of each disease apparently reflects the spatial level of expression of the mutated genes, as well as the types and positions of the mutations and their consequences at mRNA and protein levels. Identification of specific mutations in keratinization disorders has provided the basis for improved diagnosis and subclassification with prognostic implications and has formed the platform for prenatal testing and preimplantation genetic diagnosis. Finally, precise knowledge of the mutations is a prerequisite for development of gene therapy approaches to counteract, and potentially cure, these often devastating and currently intractable diseases.

Contents

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Biology of epidermal keratins

Keratins, the major constituents of epithelial cells, represent a family of about 50 proteins that form 10 nm keratin intermediate filaments and are expressed in tissue- and differentiation-specific patterns [1,2]. The intermediate filament network builds into a dense, three-dimensional and highly dynamic cytoskeleton spanning between the nucleus and the cell membrane, where they are anchored by interactions with desmosomal and hemidesmosomal linker proteins (Fig. 1). This organization provides both structural stability and flexibility, and ensures the mechanical integrity of different epithelial tissues. Keratins are expressed as obligate heterodimers of acidic (type I) and basic (type II) proteins, which assemble, through a multi-step process, into intermediate filaments (Fig. 2). The genes encoding type I and type II keratins cluster on chromosomal regions 17q12–q21 and 12q11–q13, respectively. Keratin monomers are organized as a central, alpha-helical rod of about 310 amino acids, flanked

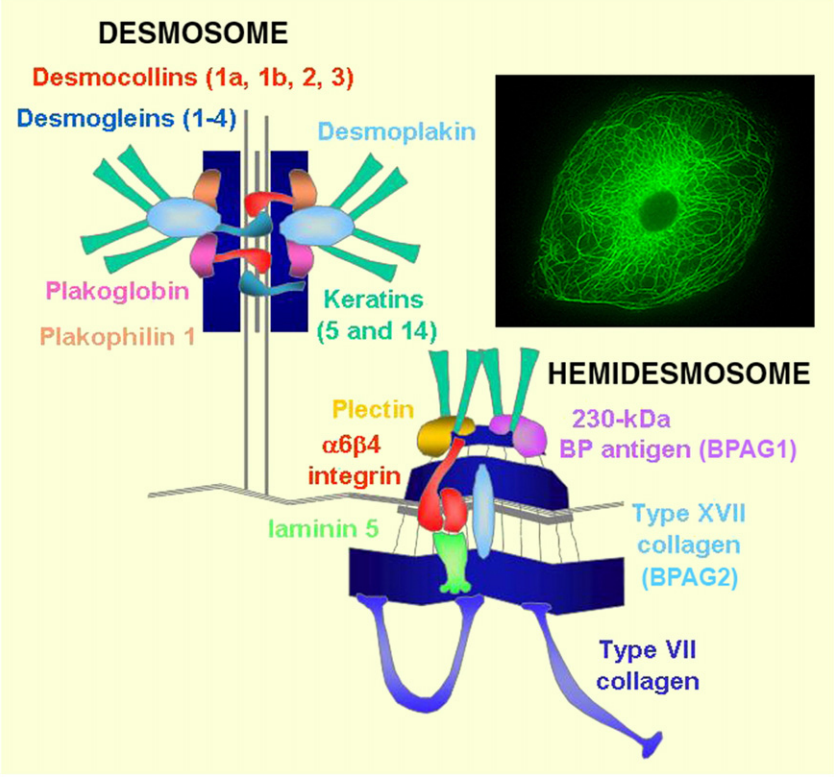

Fig. 1 – Schematic representation of the structure of desmosomes and hemidesmosomes, attachment complexes at the cell–cell and cell–matrix interface, respectively. The keratin intermediate filament network is visualized by immunofluorescence on the upper right corner. In basal keratinocytes of the epidermis, keratins 5 and 14 form the network which attaches to desmoplakin in desmosomes and to plectin in hemidesmosomes. Critical protein–protein interactions of the desmosomal and hemidesmosomal components are required for physiologic integrity of the basal layer of epidermis and its attachment to the underlying matrix or to adjacent keratinocytes, and genetic or immunologic perturbations in the hemidesmosome and/or desmosome network structures result in skin fragility.