Biochimica et Biophysica Acta xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Cell death by cornification ☆

Leopold Eckhart [a], Saskia Lippens [b,c], Erwin Tschachler [a], Wim Declercq [b,c,*]

[a] Research Division of Biology and Pathobiology of the Skin, Department of Dermatology, Medical University of Vienna, Vienna, Austria
[b] Molecular Signaling and Cell Death Unit, Department for Molecular Biomedical Research, VIB, Ghent, Belgium
[c] Molecular Cell Biology of the Skin Unit, Department of Biomedical Molecular Biology, Ghent University, Ghent, Belgium

ARTICLE INFO

Article history:
Received 19 April 2013
Received in revised form 7 June 2013
Accepted 8 June 2013
Available online xxxx

Keywords:
Keratinocyte
Cornification
Apoptosis
Necrosis
NF-κB

ABSTRACT

Epidermal keratinocytes undergo a unique form of terminal differentiation and programmed cell death known as cornification. Cornification leads to the formation of the outermost skin barrier, i.e. the cornified layer, as well as to the formation of hair and nails. Different genes are expressed in coordinated waves to provide the structural and regulatory components of cornification. Differentiation-associated keratin intermediate filaments form a complex scaffold accumulating in the cytoplasm and, upon removal of cell organelles, fill the entire cell interior mainly to provide mechanical strength. In addition, a defined set of proteins is cross-linked by transglutamination in the cell periphery to form the so-called cornified envelope. Extracellular modifications include degradation of the tight linkages between corneocytes by excreted proteases, which allows corneocyte shedding by desquamation, and stacking and modification of the excreted lipids that fill the intercellular spaces between corneocytes to provide a water-repellant barrier. In hard skin appendages such as hair and nails these tight intercorneocyte connections remain permanent. Various lines of evidence exist for a role of organelle disintegration, proteases, nucleases, and transglutaminases contributing to the actual cell death event. However, many mechanistic aspects of kearatinocyte death during cornification remain elusive. Importantly, it has recently become clear that keratinocytes activate anti-apoptotic and anti-necroptotic pathways to prevent premature cell death during terminal differentiation. This review gives an overview of the current concept of cornification as a mode of programmed cell death and the anti-cell death mechanisms in the epidermis that secure epidermal homeostasis. This article is part of a Special Issue entitled: Cell Death Pathways.

1. Introduction

The body surface of terrestrial animals is exposed to air and to mechanical stress, both incompatible with the persistence of living cells at the direct interface between an organism and its environment. While terrestrial arthropods have evolved an exoskeleton that protects underlying living epidermal cells against desiccation and mechanical damage, terrestrial tetrapods utilize a layer of dead cell corpses and extracellular deposited material as a barrier to the environment. In addition to the role of the skin in protecting against mechanical stress and in limiting the diffusion of chemical substances, the skin is also an eminent barrier to microbial infections. A plethora of antimicrobial proteins are produced by differentiating keratinocytes in a constitutive or inducible manner that protect against bacteria, viruses, fungi and parasites [1,2]. During homeostasis the most superficial cornified layers of the outer skin barrier are continuously shed by a process called desquamation and replaced by differentiating keratinocytes derived from a pool of epidermal stem cells. Corneocytes, the building blocks of the epidermal barrier, are formed by a unique form of programmed cell death referred to as cornification.

Cornification comprises three key elements, (1) the replacement of intracellular organelles and intracellular content by a compact proteinaceous cytoskeleton, (2) the cross-linking of proteins at the cell periphery to form a cornified cell envelope, and (3) the linkage of corneocytes into a multicellular, functional but biologically dead structure. The latter is in contrast with the classical apoptotic and necrotic cell death modes that are mainly aimed to delete excessive or damaged cells. There are numerous variants of cornification that lead to different cornified structures, such as the stratum corneum of the interfollicular epidermis, the stratum corneum of palmoplantar skin, the nails, the hair shaft, the inner root sheath of the hair and the papillae of the tongue. The main focus of this review is on our current understanding of the mechanism and special features of cell death by cornification for the maintenance of the skin barrier (stratum corneum). We will also address the distinctive features of hard cornification in hair, nail and tongue.

Abbreviations: FLG, filaggrin; IKK, IκB kinase; K, keratin; KLK, kallikrein; NMFs, natural moisturizing factors; RIPK, receptor interacting protein kinase; SC, stratum corneum; SG, stratum granulosum; TAK1, TGFβ-activated kinase; TGase, transglutaminase; TNF, tumor necrosis factor; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; UCA, urocanic acid

☆ This article is part of a Special Issue entitled: Cell Death Pathways.

* Corresponding author at: Department for Molecular Biomedical Research, VIB-UGent, Technologiepark 927, 9052 Ghent, Belgium. Tel.: +32 9 33 13710; fax: +32 9 22 17673.
E-mail addresses: leopold.eckhart@meduniwien.ac.at (L. Eckhart), wim.declercq@dmbr.vib-UGent.be (W. Declercq).

0167-4889/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbamcr.2013.06.010

2. Differentiation of epidermal keratinocytes

2.1. A brief guide to keratinocyte differentiation

The structures of the epidermis and skin appendages are maintained by differentiation of keratinocytes from a pool of stem cells. The epidermal stem cells are located in the basal layer of the epidermis and in special niches of the hair follicle [3]. They give rise to transiently amplifying cells that are still located in the basal layer. By asymmetric division, proliferating keratinocytes generate cells that stop to divide and start terminal differentiation (Fig. 1). These daughter cells move into the suprabasal layers of the epidermis or into suprabasal positions in the bulge of the hair follicle. Once keratinocytes are detached from the basement membrane of the epithelium, they change their gene expression profile under the control of p63 and other transcription factors [4,5]. Instead of keratins K5 and K14, expressed by all proliferating keratinocytes, the differentiating keratinocytes of the interfollicular epidermis express K1 and K10. In the hair follicle and in the nail unit differentiating keratinocytes express cysteine-rich keratins able to form multiple disulfide bridges that confer additional mechanical strength (so-called "hair keratins"). Later during differentiation, expression of a gene cluster named the "epidermal differentiation complex" (EDC) generates proteins such as involucrin and loricrin [5,6]. Both are cross-linked by enzymes of the transglutaminase (TGase) family [7]. As the main

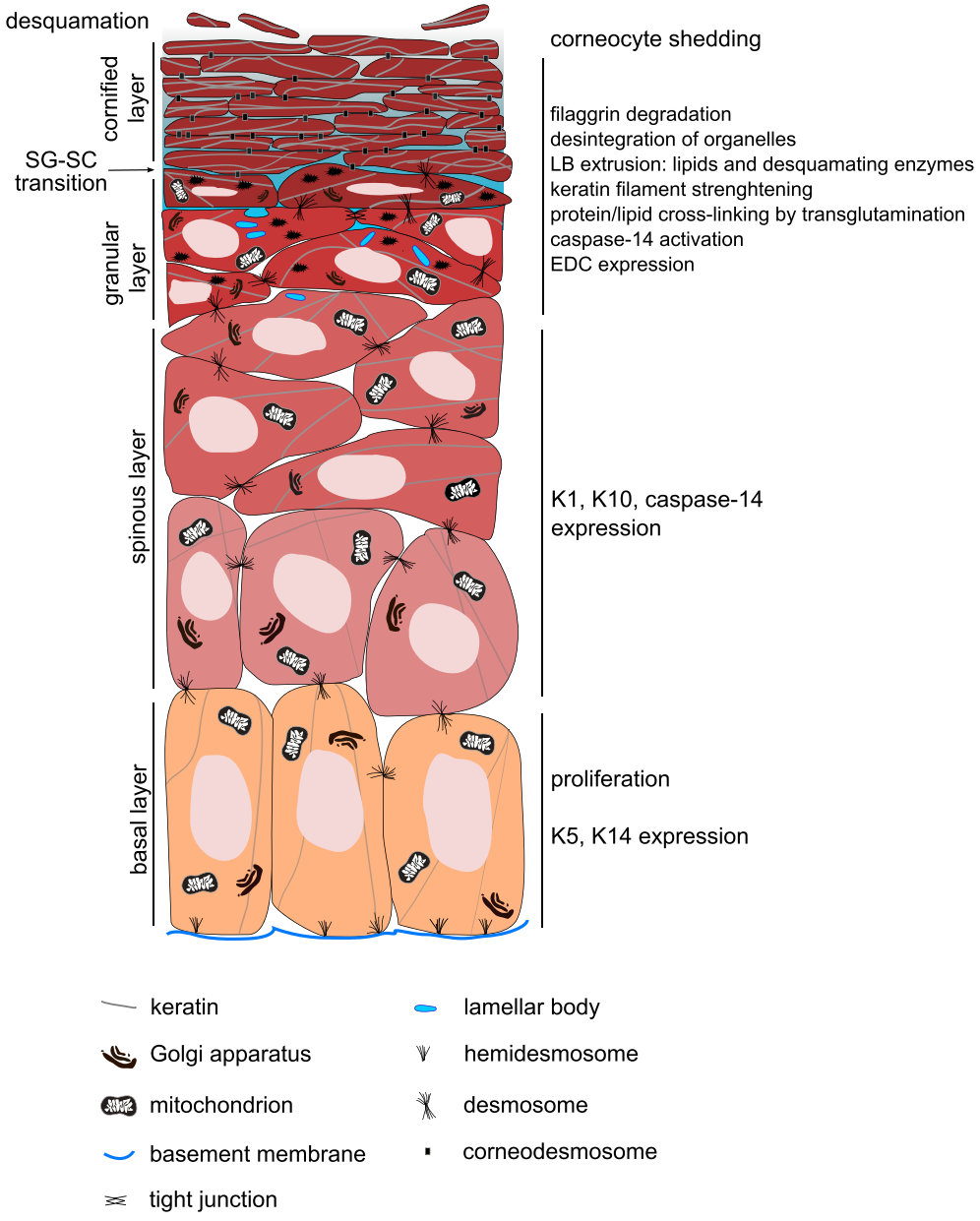

Fig. 1. The process of terminal differentiation. The epidermis consists of layers (indicated on the left) of different stages of keratinocyte differentiation distinguished by morphological hallmarks and expression markers. The cells of the basal layer are attached to the basement membrane by hemidesmosomes, have the capacity to proliferate and provide new cells that will differentiate towards the surface of the skin. Cells of the spinous layer no longer divide and express typical markers of differentiation such as keratins K1 and K10 and caspase-14. In the granular layer, keratohyalin granules are present and proteins of the epidermal differentiation complex (EDC) are expressed. At the transition from the granular to the cornified layer, a cascade of events occurs: caspase-14 becomes active and contributes to filaggrin degradation, and keratins and other proteins are cross-linked by transglutaminases. At this point the content of the lamellar bodies (LBs) is extruded into the intercellular space because the LBs fuse with the plasma membrane. At the cytoplasmic side of the plasma membrane cross-linking of proteins forms the cornified envelope (CE) that is tightly connected to neighboring CEs via corneodesmosomes. The actual physical skin barrier is formed by the tight junctions, which form strong intercellular interactions, and the lipids in the intercorneocyte spaces. Eventually the corneodesmosomes are proteolytically degraded by extracellular enzymes and the corneocytes are shed during desquamation.

Please cite this article as: L. Eckhart, et al., Cell death by cornification, Biochim. Biophys. Acta (2013), http://dx.doi.org/10.1016/j.bbamcr.2013.06.010