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REVIEW

Role of Cell Death in Differentiation of Skin Keratinocytes

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Abstract—This review examines the role of regulated cell death (RCD) in differentiation and maintenance of the barrier properties of the skin epidermis under normal and pathological conditions. The differentiation process involves activation of the mechanisms such as endoplasmic reticulum (ER) stress, macroautophagy, and corneoptosis. Responses to abiotic stresses include apoptosis, pyroptosis, necroptosis, and mitotic catastrophe. Polyploidization of keratinocytes and their transition to a senescent state could be considered as adaptive responses that preserve barrier properties of the epidermis. The balance between various forms of cell death and adaptive mechanisms – such as polyploidization and senescence is a key factor in establishing and maintaining the skin barrier function. Disruptions in this balance underlie many dermatoses and age-related changes. Understanding molecular mechanisms of these processes opens avenues for the development of the targeted therapies aimed at restoring barrier properties of the epidermis.

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INTRODUCTION

The epidermis is an outer layer of the skin, formed by a multilayered squamous cornifying epithelium and some additional cell types. It forms a complex of barrier systems (Table 1) that separate internal environment of the body from the external environment. Constant thickness and homeostasis of the epidermis are maintained through the balance between proliferative activity and death of keratinocytes. Currently, a large array of data on the mechanisms of keratinocyte differentiation has been accumulated in the scientific literature [1]. A special type of cell death, corneoptosis, is a critical component of this process [2]. However, in recent years, the data have emerged indicating that differentiation of keratinocytes involves signaling pathways of other variants of regulated cell death (RCD), as well as processes implementation of which in some cases could end in cell death (autophagy, endoplasmic reticulum (ER) stress, mitotic catastrophe). Continuous interest in studying various types of RCD in the epidermis is due to a number of factors. First, normal functioning of the epidermis involves maintenance of a balance between the types of RCD; and the processes such as autophagy, ER stress, mitotic catastrophe, and senescence are under strict control. Various factors could mediate shift of this balance, affecting differentiation process and barrier properties of the epidermis. Second, in various skin injuries and diseases, the balance shifts, and other forms of death are activated: apoptosis, necroptosis, pyroptosis, etc. When developing drugs, it is important to consider how they could affect the RCD processes necessary to maintain normal epidermal physiology. Third, involvement of many processes associated with RCD (including those recently identified in the epidermis) is still not precisely defined. Within the framework of the review, it is proposed to divide the variants of cell death in the epidermis into three groups. The first is RCD, which is a physiological variant of cell death and is necessary for the completion

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Table 1. Barrier systems of the epidermis

Some components of barrier systems	Epidermal layer	Some functions	References
Mechanical barrier			
Increased keratin content, network formation	from SB to SC	stabilization, flattening of shape	[1]
Hemidesmosomes, focal adhesions	SB	maintaining structural integrity of the layer; formation of polarity; regulation of proliferation and differentiation	[3]
Adherens junctions	SS–SG		
Desmosomes			
Tight junctions	SG2–SC	limiting permeability	[4, 5]
Corneodesmosomes	SG–SC	maintaining structural integrity of the layer; substrate for desquamation in SCd	
Intra-epidermal lipid matrix	SG2–SC	preventing water and electrolyte loss; limiting permeability	[4]
Cornified envelope proteins	SC	stabilization	[2]
Chemical barrier			
Products of secretory activity of sebaceous and sweat glands, lactate	pH < 5.5 on the SC surface	maintaining microbiome balance, participation in immune reactions and wound healing	[6, 7]
Areas with different pH in SC	pH 6.7 – upper zone of SC; pH 5.4 – middle zone of SC; pH 6.0 – lower zone of SC	regulation of differentiation, death, and desquamation; formation of intra-epidermal lipid matrix, regulation of pro-inflammatory cytokine signals, protection from pathogens, allergens, etc.	[2, 8, 9]
Natural moisturizing factor	SC	maintaining hydration	[5, 7]
Immune barrier [components of innate and adaptive immune systems]			
Pattern recognition receptors	SB	recognition of pathogens and initiation of immune responses	[4, 5]
Pro-inflammatory cytokines	SB, SS	activation of immune cells	
Antimicrobial peptides and proteins	SB–SG	protection from microorganisms, stimulation of immune cells	
Langerhans cells	SS–G2	antigen uptake, maintenance of peripheral tolerance	
T-lymphocyte populations	SB, SS	immune response, wound healing	

Table 1 (*cont.*)

Some components of barrier systems	Epidermal layer	Some functions	References
Sensory barrier			
Merkel cells	SB	perception of light touch	[3]
TRP receptors	predominantly SS–SG	perception of temperature changes, regulation of corneoptosis and permeability	[2, 10]
Photoreceptors, including opsins		perception of visible and UV radiation, regulation of proliferation and differentiation	
Piezo1 receptor		perception of sound with a frequency above 10 kHz, mechanical stress	
TAS2R receptors		regulation of differentiation	
Olfactory receptors ORs		perception of volatile components, regulation of differentiation and repair	
Radiation and antioxidant barriers			
Melanin	SB, SS	protection from UV radiation	[3]
Trans-urocanic acid	SC		[9]
Hemoglobin A	Upper layers	prevents ROS production	[11]
Biological barrier			
Microbiome (bacteria, fungi, viruses)	SC	activation of innate and adaptive immune systems; maintenance of SC homeostasis; protease synthesis	[12, 13]

of normal differentiation during cornification. The second group includes accidental and regulated forms of cell death induced by external abiotic factors (UV radiation, temperature stress, etc.). The third group includes death variants that are activated during the development of diseases. In the first group, the process of cell death participates in the maintenance of the barrier function of the epidermis. In the second group, the cell death mechanisms could lead both to elimination of the damaged cells and temporary disruption of barrier properties, and to enhancement of the barrier function. The mechanisms of death implemented in the third group most often lead to the temporary or permanent disruption of the barrier properties of the tissue. The review also discusses mitotic catastrophe and transition of the cells into a senescent state as protective mechanisms that prevent cell death and preserve barrier properties of the epidermis.

REGULATED CELL DEATH

Regulated cell death (RCD) is a critical part of both ontogenesis and normal life of an adult organism. Unlike accidental cell death – necrosis – RCD has a specific program and molecular mechanism for its implementation; as a result, it becomes possible to pharmacologically or genetically modulate this mechanism. There are three major subgroups of the RCD differing in morphology (Table 2).

The first subgroup is the so-called RCD with the morphology of apoptosis. Implementation of the apoptosis program includes induction (initiation), activation of the pro-apoptotic proteins, activation of the caspase cascade, cleavage of target molecules, destruction or rearrangement of cellular organelles, disintegration of the cell into apoptotic bodies, and their clearance by phagocytes. Caspases are cysteine proteases that cleave the target protein sequence af-

Table 2. Types of regulated cell death

Types of regulated cell death				
With the morphology of apoptosis		With the morphology of necrosis	Atypical/Non-canonical	
apoptosis	extrinsic	necroptosis	lysosomal membrane permeabilization	
	intrinsic	pyroptosis	immunogenic cell death	
anoikis		ferroptosis	cuproptosis	
oxeiptosis		necrosis due to mitochondrial permeability transition (MPT-mediated necrosis)	karyoptosis	
			NETosis/ETosis	
trogoptosis		parthanatos	cell-in-cell	cell cannibalism
				entosis
		alkaliptosis		emperipolesis
				enclysis
				phagoptosis
			paraptosis	
			metuosis	
			erebosis	
			autophagic cell death and autosis	
			corneoptosis	

Note. Types of RCD found in the epidermis and in cultured keratinocytes *in vitro* are highlighted in gray.

ter the aspartic acid residue. In humans, 11 caspases are known (caspases 1-10 and caspase-14). They are commonly divided into (pro)inflammatory (caspases-1, -4, and -5) and apoptotic [14]. Among the latter, in turn, initiator (caspase-2,-8,-9,-10) and effector (caspase-3,-6,-7) are distinguished. The caspase-14 is expressed predominantly in epidermal keratinocytes; its activation is associated with corneoptosis. Apoptosis can occur through extrinsic and intrinsic mechanisms. For the induction of the extrinsic mechanism, activation of the death receptors (for example, Fas-R or TNFR) in the plasma membrane is necessary. A multimolecular activation platform is assembled on the cytoplasmic side with participation of the adaptor proteins for activation of procaspase-8. The active caspase-8 carries out proteolysis of the effector caspases. The intrinsic pathway of apoptosis is associated with the receiving of a cell death signal from the organelles. In the mitochondrial apoptotic pathway, there is the outer mitochondrial membrane permeabilization and release of the proteins of the intermembrane space, including cytochrome *c*, into the cytosol. Together with the cytosolic protein Apaf-1, cytochrome *c* forms a multimolecular platform (apoptosome) for the caspase-9 activation. Caspase-9 cleaves and activates the effector caspases [15]. The internal pathway of apoptosis could also be initiated during endoplasmic reticulum (ER) stress – accumulation of misfolded or defective proteins in the ER lumen [16]. Activation of the signaling cascades of the unfolded protein response (UPR) reduces the overall level of translation, enhances ER-associated proteasomal degradation of proteins, and increases expression of the chaperones necessary for protein folding. UPR could also stimulate autophagy, and in the case of severe or prolonged ER stress, cause apoptotic death [17].

Anoikis is a form of apoptosis that is triggered when a cell loses contact with the substrate. Induction of anoikis is mediated by the integrins and the PI3K–Akt signaling cascade [18].

The second subgroup is RCD with necrotic morphology, in which the membrane ruptures and intracellular components end up outside the cell, activating the process of inflammation. Necroptosis is a regulated necrosis that occurs with participation of the kinases RIP1, RIP3, and the pseudokinase MLKL, which disrupts integrity of the plasma membrane [19]. Pyroptosis is initiated by the pro-inflammatory caspases; the gasdermin proteins form pores in the membrane [20]. Ferroptosis is an iron-dependent type of RCD associated with accumulation of the lipid peroxidation and oxidative stress products [21]. In the MPT-mediated necrosis, the key event is both mitochondrial membranes permeabilization, which leads to dissipation of the mitochondrial membrane potential [22]. Parthanatos occurs as a result of excessive activation of the DNA repair enzyme PARP1 (poly(ADP-ribose) polymerase 1) [23]. Alkalptosis is associated with the effect of strong bases on the cell, and death in this case occurs as a result of alkalization [24].

The third type of RCD includes various morphologically diverse types of death. NETosis/ETosis is accompanied by the release of chromatin nets decorated with antimicrobial proteins into the extracellular space, which act as traps for pathogens [25]. Metuosis and paraptosis are characterized by cytoplasm vacuolization [26]. Karyoptosis is a death associated with rupture of the nuclear envelope [27]. A separate morphological group of RCD types is associated with formation of the “cell-in-cell” structures [28]. Autophagic cell death occurs with excessive activation of the autophagy apparatus, leading to the cell digesting its own components, which becomes the cause of its death. It should be noted that the autophagic death itself is rare, although autophagy as a process could accompany other types of RCD, such as apoptosis. Cell death is considered autophagic only if it can be prevented by the chemical or genetic inhibition of autophagy [29]. As a separate type of death, autosis is also recognized as an autophagic cell death with participation of the Na^+/K^+-ATPase [30].

Mitotic catastrophe was previously considered a separate type of RCD. Inducers of mitotic catastrophe are DNA damage and/or disruption of spindle formation. Cell death could occur either directly during mitosis or after exiting division. In this case, exit is possible both in the prometaphase (mitotic slippage) and after the completion of mitosis in the next G1 period of the cell cycle [31]. Cells that have undergone pathological mitosis are tetraploid and often contain micronuclei [32]. Mitotic catastrophe could initiate such types of RCD as apoptosis and necrosis, stimulate autophagy, or transition of the cells into a senescent state [31].

Despite the variety of RCD types known to date, far from all of them are found in the epidermis. A number of studies have shown that keratinocytes are capable of realizing RCD programs with the morphology of apoptosis [33], with the morphology of necrosis [18], and with non-canonical morphology [18, 34] (Table 2). Perhaps some types of RCD have yet to be described in keratinocytes.

CELL DEATH OF KERATINOCYTES DURING THE DIFFERENTIATION PROCESS

Structure of the epidermis. The epidermis of mammals consists of several layers: basal (stratum basale, SB), spinous (stratum spinosum, SS), granular (stratum granulosum, SG) (divided into three sublayers: SG3, SG2, and SG1), and cornified (stratum corneum, SC). SC is divided into two sublayers: the inner stratum compactum (SCc) and the outer stratum disjunctum (SCd), where cell contacts are destroyed and subsequent cell detachment occurs (Fig. 1). In the thick skin (soles, palms), an additional lucid layer (stratum lucidum, SL) is distinguished between the granular and cornified layers. Each layer expresses different sets of keratin intermediate filaments in the form of heterodimers of acidic (type 1) and basic (type 2) proteins [4].

Keratinocytes are dominant cell type in the epidermis. In the basal layer, they actively proliferate, and upon separation from the basal membrane and movement to the overlying layers, they coordinately undergo successive stages of terminal differentiation, leading to formation of the outer cornified layer from the dead cornified cell envelopes (corneocytes/cornified scales) in the form of a flattened tetrakaidecahedron (Kelvin tetrakaidecahedron) [2]. Formation of mature corneocytes is preceded by degradation of the membrane organelles and cytosolic proteins, with exception of cyokeratins [1]. Despite the fact that SC consists of dead cell envelopes, it remains functionally active, since, by interacting with the external environment, it performs barrier functions and is the first line of skin defense [9]. Dead corneocytes undergo pH-dependent desquamation (shedding) in SC. Thus, regulated cell death is the final stage of keratinocyte differentiation in the epidermis.

Main stages of keratinocyte differentiation in the epidermis. Evolutionarily, keratinocyte differentiation is accompanied by cornification, which arose in connection with the need to retain moisture in the internal environment of the first terrestrial vertebrates [4]. In the process of direct contacts of the abiotic and biotic environment factors (temperature, humidity, ultraviolet radiation, pathogens, etc.) with the skin, the skin epidermis forms complex systems of mechanical, chemical, immune, sensory, radiation, and antioxidant barriers (Table 1). Maintaining an

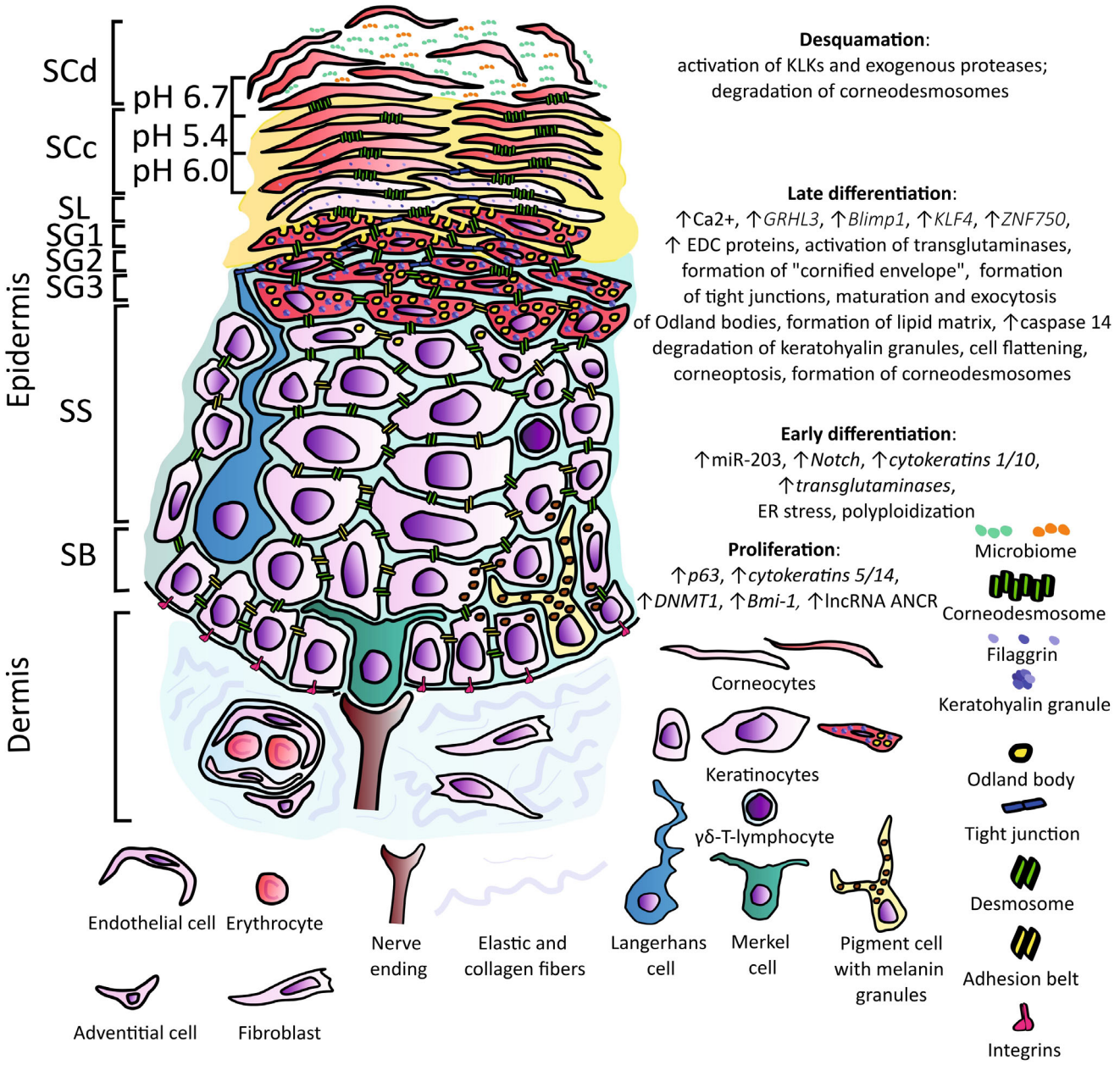

Fig. 1. Organization of epidermis. Main stages of differentiation.

undifferentiated state and subsequent transition to differentiation depends on the changes in chromatin structure and is strictly regulated by activation/suppression of the expression of many factors [1]. Undifferentiated keratinocytes in the SB express keratins-5/-14. Suppression of the genes of differentiation is facilitated by, among other things, the Polycomb group protein Bmi-1, DNA methyltransferase 1 (DNMT1), and long non-coding RNA (lncRNA) ANCR [35]. After losing contact with the basal membrane, the cells move from SB to SS and carry out the differentiation program. Decrease in the expression of integrins, p63, activation of the Notch signaling pathway, and a number of other factors contribute to the appearance of early differentiation markers (keratins-1/-10) and decrease in proliferative activity [3, 35]. Also, in SS, there is an increase in the cell and nucleus sizes and polyploidization [36, 37]. When transitioning from SS to SG, several transcription factors (including GRHL3, Blimp1, KLF4, ZNF750) and chromatin remodelers are activated, which, in turn, stimulate expression of the specific proteins whose genes are located in the epidermal differentiation complex (EDC): loricrin, involucrin, elafin, periplakin, envoplakin, etc. [1]. Additionally, events occur that are associated with the increased ER stress, autophagy, lysosome biogenesis, and Golgi apparatus fragmentation [38].

Two types of granules are found in SG. The first type (keratohyalin granules) is not surrounded by a membrane, interacts with the keratin-1/-10 network, and is a biomolecular condensate of the profilaggrin protein [39]. The second type (Odland granules/lamellar bodies) branches off from the Golgi apparatus, is surrounded by a membrane, and contains stacks of lipid bilayers of phospholipids, glucosylceramides, sphingomyelin, and cholesterol, as well as a set of enzymes and their inhibitors. During secretion, the contents of Odland granules enter the intercellular space of SG1 and form an intra-epidermal lipid matrix in which the SG1 keratinocytes and SC corneocytes are embedded [39]. Various enzymes are activated at different pH values in the SC and participate in degradation of the specialized intercellular compounds (corneodesmosomes) during desquamation. When transitioning from SG to SC, the EDC complex proteins form the cornified envelope – a net-like layer beneath the plasma membrane added to it by the transglutaminase enzymes [4]. Filaggrin breaks down into individual amino acids with high hygroscopicity (natural moisturizing factor) in the middle layers of SC. Desquamation includes destruction of corneodesmosomes by the kallikrein-like peptidases (KLK) [8, 14].

The role of cell death in physiological differentiation of keratinocytes. The entire complex of events, from the loss of a keratinocyte connection with the basal membrane to desquamation of a corneocyte, is commonly called cornification [40]. The initial event of these processes is activation of the specialized keratinocyte RCD in the SG1 [2]. Until recently, it was believed that the physiological cell death in SG1 is the result of implementation of the apoptosis program with some features [41]. However, this was contradicted by a number of facts, including absence of activity of the classical apoptotic caspases in the differentiating keratinocytes, activation of the anti-apoptotic transcription factor NF-κB, etc. [1, 4, 40]. Recently, a group of Japanese researchers identified unique features accompanying the death of keratinocytes in the SG1 in mice and based on this introduced a new term, “corneoptosis” [2]. Implementation of the first phase of the corneoptosis program occurs under conditions of a single prolonged increase in the intracellular calcium concentration at a neutral pH, followed by cytoplasm acidification. Increase in the calcium levels and following acidification leads to a sharp stop in the movement of low pH vesicles, mitochondria, and is accompanied by a drop in the mitochondrial membrane potential [42]. The mechanism that ensures increase in the calcium levels is currently not fully understood. On the one hand, TRPV family calcium channels, which are responsible for the intake of exogenous calcium, could be involved in this process [2]; on the other hand, calcium ions could come from the endogenous depots – ER or mitochondria. In the second phase of corneoptosis, acidification of the cytoplasm stimulates activation of the enzymes, including DNases, as well as degradation of the keratohyalin granules, release of filaggrin from them, and its dispersed distribution throughout the cytoplasm. The protein “glues” (tightly bundles) cytokeratins together, which leads to the rapid (within 10 min) flattening of the cells [2, 8]. In parallel with the change in the shape of the keratinocyte, the nucleus elongates and compresses, and organelle degradation begins [42]. It has been shown that the ER, nuclei, mitochondria, presumably parts of the Golgi apparatus not associated with Odland granules, as well as many cytosolic proteins, are removed from the keratinocytes in SG by macroautophagy [1]. The removal of mitochondria depends on activation of the mitophagy receptor NIX and the GTPase DRP1 [42]. Destruction of the substrates during differentiation could be associated not only with the activation of autophagy. Changing the patterns of keratin expression is one of the events of early differentiation. When the cells move from the basal to the spinous layer, the ubiquitin ligase Kelch-like family member 24 (KLHL24) directs keratins-14 and -15 (specific to basal layer cells) for degradation in proteasomes [1]. Corneoptosis is accompanied by degradation with participation of the enzymes, including keratinocyte-specific DNase 1L2, lysosomal DNase 2, as well as caspase-14 and SASPase, which are involved in the cleavage of profilaggrin [42].

Interestingly, it seems that the signaling pathways of other variants of the cell death could be also involved in cornification. Keratinocytes are the only cell type that expresses all types of the pore-forming gasdermin proteins, which serve as key effectors of the pyroptotic cell death. It has been shown that differentiation of the human keratinocytes *in vitro* includes expression of certain members of gene families associated with pyroptosis and inflammatory signaling pathways (including gasdermins A, D, and several interleukins 1), and the level of their expression depended on the stage of differentiation [43].

ER stress in normal differentiation. Low physiological level of UPR is observed in many tissues of the body and is necessary for normal differentiation of the cells, including keratinocytes [44]. Expression of UPR markers, proteins GRP78 and HRD1, is characteristic of the differentiating keratinocytes of SS and skin equivalents [45]. It has also been shown that the chemically induced ER stress leads to increase in the expression of differentiation markers, including ABCA12, KLF4, C/EBPβ, involucrin, and filaggrin, in the primary keratinocytes, HaCaT cells, and epidermal tumor cell lines *in vitro*. Activity of the signaling

molecules ATF4, ATF6, and XBP1 is necessary for the expression of these markers [45-47]. ER stress could also lead to the increased autophagy as a compensatory mechanism aimed at cell survival [47].

UPR could also play a role in the keratinocyte differentiation by regulating calcium signaling. Calcium gradient is maintained in the epidermis; its concentration is lowest in the basal layer and gradually increases toward the granular layer [47]. The release of calcium ions from the ER in SG cells leads to activation of the UPR marker XBP1s and stimulation of terminal differentiation, increased expression of loricrin and caspase-14. Exposure to thapsigargin, an inhibitor of the Ca^{2+} ATPase SERCA2 and inducer of ER stress, also leads to stimulation of terminal differentiation in the epidermis [48, 49]. It remains unclear what contribution these processes make to the activation of corneoptosis.

Thus, the main type of death that ensures normal differentiation of keratinocytes is corneoptosis, accompanied by a disruption of the apoptosis program [41]. At the same time, molecular pathways characteristic of other variants of cell death (pyroptosis) or processes that could lead to cell death (autophagy, ER stress) are activated. Currently, it remains unclear to what extent these pathways are necessary for epidermal differentiation. Studying the structure of epidermis in the transgenic animals could answer this question, but knockout of the RCD genes affects the development of the organism as a whole. Nevertheless, a number of works have shown that in mice with anti-apoptotic proteins overexpression, structure of the epidermis is not disrupted [50]. Knockout of the caspase-3 [51] or the regulator of the extrinsic pathway of apoptosis activation FADD [52] leads to hyperplasia of the epidermis, disruption of differentiation, and activation of necroptosis. Knockout of the necroptosis regulator RIPK1 also causes hyperplasia and differentiation disorders [53]. Experiments with knockout of the autophagy genes in mice have shown no changes in the structure of the epidermis [54]. However, in this case, keratinocytes become more sensitive to stresses and more easily transition to a senescent state [55]. Knockout of Ire1, which regulates ER stress, does not affect the structure of epidermis but causes increase in apoptosis after UV exposure [56]. Based on these data, it can be assumed that the molecular mechanisms of apoptotic death and necroptosis could be involved in the regulation of keratinocyte differentiation, while autophagy and ER stress are rather necessary for the repair processes. However, these data contradict modern ideas: it is assumed that the apoptotic death program is not involved in corneoptosis, and autophagy is necessary for degradation of the organelles during corneoptosis.

KERATINOCYTE DEATH UNDER THE INFLUENCE OF EXTERNAL ABIOTIC FACTORS

The skin is constantly exposed to various abiotic factors, such as ultraviolet (UV) radiation, temperature changes, and exposure to chemical compounds. The most significant of these is UV radiation. Photodamage to the skin causes sunburn, phototoxic and photosensitive dermatitis, and photoaging. 95% of UV radiation reaching the Earth's surface and responsible for skin aging due to the DNA damage by reactive oxygen species (ROS) is UVA. UVB contributes to skin redness and burns due to direct DNA damage. It has been shown that UV radiation in keratinocytes could cause various types of RCD, including apoptosis, pyroptosis, necroptosis, and autophagic death [33].

Apoptosis. Apoptosis is the most frequently occurring form of RCD in keratinocytes under the influence of abiotic factors, including UV radiation. In this case, both the extrinsic and the intrinsic pathways of death are activated. In the case of photodamage to the skin by UV rays, Fas binds to its ligand FasL, trimerizes, and triggers apoptosis through the receptor-mediated mechanism. In addition, UVB activates Fas directly, without the involvement of FasL. UVB could also enhance the receptor apoptotic pathway in keratinocytes by inducing expression of the adaptor protein FADD [33, 57]. The intrinsic pathway of apoptosis activation is primarily due to accumulation of active forms of oxygen, which cause DNA damage. Therefore, antioxidants could be used as inhibitors of apoptosis [33, 57].

UVB, by damaging DNA, induces activation of the tumor suppressor p53, which first causes cell cycle arrest in the G1 phase, giving time for DNA repair. If the damage is irreversible, p53 could trigger both the receptor and the mitochondrial pathway of apoptotic death, since both the Fas receptor ligand and the pro-apoptotic protein Bax, capable of inducing of the outer mitochondrial membrane permeabilization, are under the transcriptional control of p53. Interestingly, the p53-mediated activation of apoptosis on UV irradiation occurs primarily in the keratinocytes of the SB layer. In the SS layer, the cells repair DNA more successfully, and the cell death is less pronounced. It is assumed that such resistance of keratinocytes could be associated with the process of cell senescence in the SS layer [58].

UVB irradiation could also involve the intrinsic pathway of keratinocyte apoptosis activation through activation of the upstream MAPK kinases under oxidative stress. It is known that the components of the MAPK kinase cascade, JNK, and p38 can directly phosphorylate p53 and induce the FasL expression [33]. The mitochondrial pathway of apoptosis is

also involved in the response of the skin epidermis to UV exposure. It has been shown that Bax promotes apoptosis, while the anti-apoptotic protein Bcl-2 inhibits the UVB-induced apoptosis [33].

Pyroptosis. UV radiation could also activate other forms of death, including pyroptosis. Under the influence of UV radiation, large protein complexes – inflammasomes – are formed in keratinocytes. Under exposure to UVB irradiation, expression of their components, NLRP1 and NLRP3, significantly increases in keratinocytes. These complexes activate pro-inflammatory caspases-1 and -4 [20]. Pro-inflammatory caspases, on the one hand, contribute to the maturation of pro-IL-1β. On the other hand, these caspases process gasdermin proteins. Gasdermins form pores in the keratinocyte membranes, disrupting their permeability. Cell death by pyroptosis has a necrotic morphology and is accompanied by the development of an inflammatory response [20].

Necroptosis. Inflammation also accompanies necroptosis, which could be activated in response to UVB due to increased expression of TNFα [59]. UVA also activates autophagy processes, which ensure removal of the membrane components containing oxidized lipids, removal of the protein aggregates and melanin granules in keratinocytes [33].

Thermal damage (burns). Another significant abiotic damaging factor for the skin epidermis are burns. Exposure to high temperatures could cause both unregulated necrosis and, at sublethal temperature values, RCD [59]. In the experiments with cultured primary keratinocytes, heating to 60°C showed that the number of apoptotic cells increases with the increasing incubation time. Involvement of the receptor pathway of apoptosis in the burn injuries is indicated by accumulation of the FasL, TRAIL, and TNFα ligands in the blister fluid. *In vitro*, active caspase-8 is detected in the keratinocytes under thermal stress [59]. Immunohistochemical studies of the skin after burns *in vivo* have shown presence of the active forms of caspases-3 and -8, Fas, TNFR1, and the TRPV channel. In some works, the APAF1 immunoreactivity is described, while in others, involvement of APAF1 and cytochrome *c* is disputed [59].

Human keratinocytes express temperature-sensitive voltage-dependent ion channels TRPV1 and TRPV2 (transient receptor potential vanilloid channels), which are stimulated by heating to >43°C and >52°C, respectively. Their opening leads to increase in the intracellular calcium concentration, which affects functional activity of mitochondria [10]. When keratinocytes are damaged by the exposure to high temperatures, a caspase-independent pathway of apoptosis with involvement of AIF/EndoG is triggered [60]. Interestingly, the related ion channel TRPV3 is involved in the regulation of keratinocyte proliferation with moderate activation. Strong activation of TRPV3 could cause cell death [61].

It has also been shown that burns induce the receptor-mediated activation of RIP3 (receptor-interacting serine/threonine-protein kinase 3), indicating necroptosis [62]. However, inhibition of necroptosis does not reduce the level of cell death in the skin after a burn: perhaps necroptosis does not play a key role in this process; one cannot also exclude switching to other types of cell death [59].

Entosis. Another possible mechanism of keratinocyte death is entosis. In entosis, one epithelial cell with damage invades another [28]. Entosis has been shown in the culture of immortalized human keratinocytes HaCaT [34]. In the composition of the epidermis under normal conditions, the “cell-in-cell” patterns are not detected. However, with the hyper-expression of spastin (a protein that destroys microtubules) in the SS and SG layers, entotic structures appear. In this case, formation of desmosomes is disrupted, proliferation of the SB layer cells is enhanced, and the epidermis thickens [63]. Cell-in-cell structures are also detected after the knockout of the oncogene matriptase 1 (ST14) in the non-cornifying epithelium of zebrafish [64].

KERATINOCYTE DEATH IN PATHOLOGIES

Skin pathologies (dermatoses) comprise a large group of inflammatory, infectious, autoimmune, parasitic, and genetic diseases that affect the skin. Such conditions include atopic dermatitis, rosacea, acne, and psoriasis. Most of them are not associated with RCD, specifically with the death of keratinocytes. An exception is psoriasis, an autoimmune disease characterized by the appearance of convex, dry plaques on the skin – papules. Papules are sites of chronic inflammation, impaired differentiation, and increased proliferation of keratinocytes [65]. In psoriasis, decrease in apoptotic activity, autophagy, and suppression of ER stress is observed, which could negatively affect differentiation. At the same time, the RCD forms with predominantly necrotic morphology are activated [18].

Necroptosis. Necroptosis plays a major role in the pathogenesis of psoriasis. In all layers of the epidermis of affected skin areas, there is a significant increase in the expression of RIPK1 and MLKL, while RIPK3 and phosphorylated MLKL are mainly expressed in the keratinocytes located in the upper layers [66]. Inhibitors of necroptosis, R-7-Cl-O-necrostatin-1 (Nec-1s) and necrosulfonamide (NSA), which act on RIPK1 and MLKL, respectively, effectively suppress necroptosis in the mouse model with imiquimod-induced psoriasis [67].

Pyroptosis. In psoriasis, the level of expression of gasdermin D (GSDMD) is increased in the affected areas of human skin. Increase in the concentration of GSDMD, IL-1β, and cleaved caspase-1 targets is detected both in the epidermis of mice with imiquimod-induced psoriasis-like dermatitis (IIPLD) and in the keratinocytes *in vitro* treated with M5, which stimulates psoriatic inflammation. In the keratinocytes with the Gsdmd$^{-/-}$ genotype, pyroptotic morphology is not detected after stimulation with M5 [18]. Also, during pyroptosis, the level of expression of GSDME increases, and in the Gsdme$^{-/-}$ mice, the levels of expression of pro-inflammatory cytokines are reduced and the skin inflammation is suppressed [18, 68].

Parthanatos. Involvement of parthanatos in the pathogenesis of psoriasis has been shown. Thus, in the affected skin areas of the patients with psoriasis, there is hyper-expression of NAMPT (nicotinamide phosphoribosyl transferase, an enzyme that synthesizes NAD^+) in the cells of the SS and, to a lesser extent, the SB layers, as well as increased activity of PARP and translocation of the mitochondrial AIF (AIFM1) into the nucleus. Inhibition of the NADPH oxidase–NAMPT–PARP–AIFM1 pathway reduces oxidative stress, DNA damage, inflammation, hyperproliferation, and death of keratinocytes in the organotypic 3D models of human skin affected by psoriasis [69].

Ferroptosis. In the cultures of primary human keratinocytes treated with erastin and in the mouse model of psoriasis, signs of ferroptosis are detected. In the keratinocytes, the single-cell analysis revealed correlation between the lipid oxidation and the Th22/Th17 response. In addition, the ferroptosis inhibitor-1 (Fer-1), a potential inhibitor of lipid peroxidation, weakens the signs of ferroptosis in the keratinocytes treated with erastin and reduces the psoriasis-like dermatitis induced by the imiquimod exposure in the mouse model. Fer-1 also showed a significant anti-inflammatory effect *in vitro* and *in vivo*, which indicates complex interaction between the iron metabolism, lipid peroxidation, and antioxidant defense systems during the ferroptotic death of keratinocytes, which may have potential therapeutic significance.

Cuproptosis. Transcriptomic analysis revealed significant increase in the expression of the genes associated with cuproptosis (MTF1, ATP7B, and SLC31A1) in the patients with psoriasis. In additional clinical studies, an increased copper content in the blood serum was found. Copper uptake by the cells is mainly regulated through the IL-17–STEAP4 pathway; and the patients with psoriasis have increased levels of the STEAP4 expression.

Oxeiptosis. It has been found that in the psoriasis-affected skin, oxeiptosis is suppressed due to the high level of expression of the upstream regulator KEAP1 [70].

Anoikis. In psoriasis, normal polarized distribution of the integrin expression on the cell surfaces is disrupted, which impairs cell attachment to the extracellular matrix and is a trigger for anoikis [18].

Autophagy. In psoriasis, there is a disruption of autophagy processes, which may be associated with the presence of cytokines characteristic of psoriasis. In particular, IL-17A acts through the PI3K/AKT/mTOR pathway. IL-33 suppresses autophagy through the STAT3 phosphorylation in the mouse model of psoriasis. The AhR receptor (aryl hydrocarbon receptor), when activated, also inhibits autophagy and promotes development of inflammation through the NF-κB/p38 MAPK signaling pathway by stimulating keratinocytes to secrete pro-inflammatory cytokines IL-1β, IL-6, and TNF-α. TNF-α inhibits autophagy and lysosome function. Inactivation of the proteins from the MAPK family reduces the level of autophagy in keratinocytes, which positively correlates with the severity of psoriasis in both mouse models and patients [18, 71]. In addition, in the keratinocytes with psoriasis, the level of the autophagy marker protein LC3 and the kinase ULK1 (a key protein involved in the initiation of autophagy) is reduced. At the same time, a number of researchers note increase in the expression of ATG5 and ATG7 proteins, which are necessary for elongation of the phagophore. Perhaps this is a compensatory mechanism under conditions of the reduced lysosomal activity. It is also known that the autophagy inducer rapamycin is effective in the therapy of psoriasis due to suppression of the ERK1/2 and mTOR signaling pathways [71].

ER stress. In psoriasis, decrease in the expression of ER stress markers GRP78, ATF6, and HRD1 is shown [45, 72, 73]. Cyclosporin A, used in the treatment of psoriasis, is able to cause UPR in keratinocytes, which probably contributes to its therapeutic effect [74]. ER stress is also associated with other diseases. One of them is the Darier–White disease, a hereditary disease characterized by horny papules on the seborrheic areas of the skin [75]. Mutation in the gene encoding the Ca^{2+} pump SERCA2 leads to disruption of the calcium homeostasis and chronic ER stress. In the pathological keratinocytes, there is a decrease in the transport of E-cadherin and desmosomal cadherins to the plasma membrane and their accumulation in the ER, which, in turn, leads to the increase in UPR, anoikis, and apoptosis [45, 76]. ER stress could also be involved in the pathogenesis of rosacea. Rosacea is characterized by erythema, dilation of the small facial skin vessels, and increased expression of the Toll-like receptor 2 (TLR2) and of the antimicrobial protein cathelicidin in keratinocytes [77, 78]. Activation of TLR2 by ultraviolet radiation, *Demodex* mites, or pathogens leads to the cleavage of cathelicidin and stimulates a pro-inflammatory

response and angiogenesis, leading to the development of rosacea symptoms [77]. The ER stress inducers such as tunicamycin, thapsigargin, and dithiothreitol increase the TLR2 expression in keratinocytes. Also, the factors of rosacea development themselves (UV radiation, skin irritation, and high temperatures) could stimulate ER stress [79, 80].

Thus, under abiotic damage and in the pathologies in the epidermis, different types of RCD could be simultaneously activated. Various types of RCD may be present simultaneously: for example, necroptosis, pyroptosis, parthanatosis, pyroptosis,

ferroptosis, and cuproptosis have been described in psoriasis; the combination of NLRP3-dependent pyroptosis, apoptosis, and necroptosis is termed "PANoptosis" [81]. A similar pattern is observed in the case of UV exposure [82]. In addition, switching between the different types of RCD is possible, as demonstrated in the example of PANoptosis in the mouse and human keratinocytes: inhibiting one of the death pathways does not significantly reduce proportion of the dying cells, which suggests that the suppression of one mechanism is compensated by others [82].

MAINTAINING THE BARRIER FUNCTION OF EPIDERMIS

The main function of the epidermis is to create and maintain a barrier between the body and the external environment, including under the influence of damaging factors. Therefore, activation of certain processes associated with RCD, which in other tissues lead to cell elimination, in the epidermis, on the contrary, causes enhancement of the barrier properties.

Mitotic catastrophe and polyploidization. Proliferative activity of keratinocytes in the epidermis is present in the SB and SS layers: keratinocytes exhibit such proliferation markers as Ki67, cyclins A, B, E, DNA replication, and mitotic figures [36, 37]. Therefore, various exposures to which the epidermis is subjected could cause mitotic catastrophe in both SB and SS. However, keratinocyte death directly during mitosis has not been described, possibly due to the difficulty of registering such events. At the same time, the epidermis contains cells with micronuclei (about 0.1%) [83, 84] and polyploid cells (about 30%) [36], which is indirect evidence of mitotic catastrophe. It is assumed that in the lower layers of SS, keratinocytes undergo pathological mitoses, leading to polyploidization of the cells. In the apical layers of SS, the main mechanism of polyploidization is endoreplication [37].

Currently, it is believed that at the initial stages of differentiation, keratinocytes, unlike most other types of terminally differentiating cells, do not exit the cell cycle [85]. At the later stages, cells stop at the G2/M transition, and exposures that block mitosis stimulate terminal differentiation. Cell cycle arrest is controlled by cMyc, cyclin E, and p53 [86]. The biological significance of polyploidization is apparently to increase the size of keratinocytes in the upper layers of the epidermis, which increases their resistance to abiotic damage and also contributes to accumulation of RNA and proteins for the differentiation process. Thus, mitotic catastrophe, through which a significant number of keratinocytes may pass, does not induce the cell death but, on the contrary, contributes to the maintenance of the barrier function of the epidermis.

Cellular senescence. Cellular senescence is one of the mechanisms of cell elimination that participates in the removal of damaged cells, suppression of tumor growth, and tissue remodeling. Cells enter a state of senescence in response to various damages. In this case, cells stop progressing through the cell cycle and acquire a number of characteristic features. Elimination of the cells is due to their specific secretory phenotype (SASP – senescence-associated secretory phenotype), which causes development of a local inflammatory response and destruction of the senescent cells by the immune system [87]. There are several mechanisms that activate the process of cellular senescence [88], two of which are implemented in the epidermis.

Stress-induced senescence (SIS) develops under the influence of various damaging factors [88]. In the case of significant damage, cell cycle arrest is mediated by activation of the transcription factor p53 and the cell cycle inhibitor protein $p21^{WAF1/CIP1}$ controlled by it. Low-level damage activates the stress kinase p38 signaling cascade, which activates the cell cycle inhibitor $p16^{INK4A}$.

The second mechanism of keratinocyte transition to the senescent state, **oncogene-induced senescence (OIS)**, is associated with activation of oncogenes. In particular, in psoriasis, activation of the Ras oncogene is noted [89]. In this case, the cell cycle arrest is mediated by the p38-p16 signaling cascade. Classic replicative senescence does not occur in keratinocytes for unknown reasons [90]. The number of senescent keratinocytes increases with age [91]. The senescent keratinocytes contain various markers, such as Sen-β-Gal, $p16^{INK4A}$, $p21^{WAF1/CIP1}$, H2A.J, loss of lamin B1, and HMGB1 [90, 92-95].

Apparently, in the epidermis, two mechanisms of senescence are independently implemented in different cells: the $p21^{WAF1/CIP1}$-dependent and the $p16^{INK4A}$-dependent. The data from the single-cell DNA sequencing of the intact human epidermis have shown that the $p21^{WAF1/CIP1}$+ and $p16^{INK4A}$ + cells represent two different populations, each with its own unique SASP [96]. Immunocytochemical staining of the intact skin reveals single $p16^{INK4A}$+ cells in the

lower layers of the epidermis, while more numerous $p21^{WAF1/CIP1}$+ cells are detected in the upper layers of the epidermis [96]. Activation of SASP in keratinocytes is mediated by the transcription factor NF-κB [97].

The fate of individual senescent keratinocytes is currently unknown. Involvement of immune system cells in their elimination has not been shown. Death of the senescent keratinocytes could occur through autophagy. Thus, in the model of senescence of the primary keratinocytes, accumulation of the autophagy markers (Beclin1 and LAMP1) and autophagic death was revealed [98]. In the composition of the epidermis, autophagic death of the senescent cells has not been shown, possibly due to detection difficulties. However, removal of the senescent cells during desquamation seems more likely. It is not clear whether this process is accompanied by the acquisition of any signs of differentiation. There are no data in the literature on colocalization of the senescence markers and differentiation markers (cytokeratin 10, involucrin, loricrin, filaggrin) in the epidermis. But in the monolayer culture and in the low-differentiated organoids, some keratinocytes could simultaneously contain senescence markers (Sen-β-Gal) and differentiation markers (cytokeratin 10/involucrin) [99]. Since the cells in the upper layers of the epidermis (SG1) usually look homogeneous, it is most likely that the senescent cells undergo corneoptosis.

Transition of keratinocytes to the senescent state is associated with certain pathological conditions of the skin. It has been shown that the keratinocytes characterized by the expression of $p16^{INK4A}$ secrete SASP, which has a paracrine effect on the neighboring cells. Such SASP components as IL-6, IL-8, and Wnt [100, 101] stimulate proliferation of the neighboring keratinocytes and contribute to hyperplasia and papilloma growth [100, 102]. In the area of actinic keratosis, there are also keratinocytes expressing $p16^{INK4A}$ [100]. These same SASP components could affect metastasis: the conditioned medium obtained from the culture of senescent primary keratinocytes after UV exposure accelerates migration of the human epidermoid carcinoma A431 cells [101]. Other SASP components, Insulin-like Growth Factor-Binding Protein 3 (IGFBP3) and Nerve Growth Factor (NGF), stimulate proliferation of melanocytes in the areas of epidermis with hyperpigmentation (melasma, solar lentigo) [103]. Cells with the signs of senescence are also found in psoriasis [89, 104]. In this case, the cell cycle arrest is mediated by activation of both $p16^{INK4A}$ and $p21^{WAF1/CIP1}$, and the SASP of the senescent keratinocytes differs from the SASP in keratosis and contains such pro-inflammatory cytokines as TNF-α, as well as IL-6 and IL-1β. It is assumed that transition of keratinocytes to the senescent state in psoriasis serves, on the one hand, to maintain the inflammatory response and, on the other hand, to enhance proliferation of keratinocytes.

Presence of the senescent cells in the epidermis is important for preserving barrier properties. Damage that activates RCD in other tissues causes keratinocytes to transition to a senescent state, one of the distinctive features of which is increased resistance to apoptosis [105]. In the composition of normal epidermis, the response to SASP does not have time to develop, as senescent cells are removed during desquamation. However, with age, the rate of epidermis renewal slows down [106]. The senescent cells remaining in the epidermis for a long time due to the specific secretome SASP, stimulate proliferation of the neighboring cells, causing hyperplasia and hyperpigmentation. In some cases, hyperplasia could lead to the development of tumors, as the foci of the cells containing mutations, for example, areas with the mutant p53, appear in the epidermis with age [107]. Activation of proliferation of such cells poses the greatest threat. Thus, in the young skin, transition of the cells to a senescent state is a protective reaction that allows preserving integrity of the cell layer. With age, senescent cells could stimulate hyperplasia of the epidermis.

CONCLUSION

Epidermis is a complex multicomponent system (mechanical, chemical, immune, and biological barriers) that has been evolutionarily formed to isolate internal environment of the body from the aggressive abiotic and biotic factors. The main features of terminal keratinocyte differentiation are:

- entry into differentiation without exiting the cell cycle, exiting the cell cycle at the G2/M stage at the late differentiation stages;
- a special type of cell death, corneoptosis;
- involvement of molecular mechanisms of RCD (pyroptosis, autophagy, ER stress) in differentiation and maintenance of barrier properties;
- disruption of apoptotic death in SS and SG;
- polyploidization of some cells with involvement of mitotic catastrophe and endoreplication;
- transition of damaged cells to a senescent state;
- simultaneous activation of different death mechanisms under abiotic stresses and skin pathologies.

The balance between various forms of cell death involved in differentiation processes and in the process of eliminating damaged cells is a critical factor in maintaining the barrier function of the epidermis (Fig. 2). Physiological death during corneoptosis creates the barrier and involves the use of such molecular components of RCD as autophagy, ER stress,

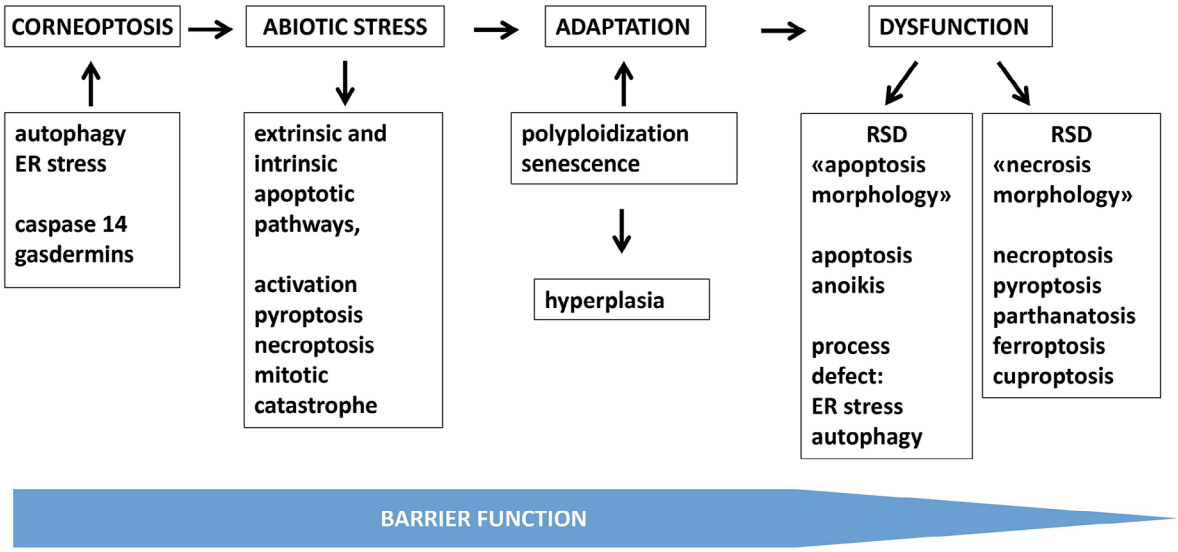

Fig. 2. The role of various regulated cell death pathways in maintaining barrier function of the epidermis.

and pyroptosis. Although, involvement of apoptotic processes is still a controversial issue.

Constant exposure to abiotic factors inevitably leads to various damages to keratinocytes. In other tissues, such damage initiates cell death. However, in the epidermis, massive death would lead to a critical disruption of barrier properties. As an evolutionary adaptation, alternative programs are activated in keratinocytes: polyploidization and transition to a senescent state in SS. In the cases where compensatory mechanisms are insufficient, there is a switch to pathological variants of RCD. In the RCD with apoptotic morphology, the possibility of repair and restoration of the barrier properties is preserved. The RCD with necrotic morphology is accompanied by the secretion of pro-inflammatory cytokines and disruption of the integrity of plasma membranes, which leads to the barrier disintegration (Fig. 2).

We suggest the following promising areas for studying the role of RCD in the functioning of epidermis as a barrier structure:

1. Currently, models of transgenic animals have been developed in which the gene of interest is placed under the promoter of keratins or other differentiation markers expressed in different layers of the epidermis [63, 108]. Using the Cre-lox system, it is possible to inactivate genes controlling different types of RCD in different layers of the epidermis, which would make it possible to answer the question about the role of various molecular mechanisms of RCD in the differentiation of keratinocytes.
2. In recent years, the data have appeared indicating that the physiological level of ER stress is capable of stimulating differentiation of some cell types [44]. We assume that the role of ER stress in the induction of the keratinocyte differentiation may turn out to be more significant than it seems at present: ER stress is involved in the regulation of Ca^{2+} ion levels, which is the initial event of corneoptosis. By regulating the level of ER stress, it is possible to influence corneoptosis, accelerating or suppressing it.
3. Under abiotic damage and in the epidermal pathologies, different RCD pathways are simultaneously activated. Which types of death are the main and leading ones in this case remains unclear. By changing the balance of different molecular mechanisms of RCD, it could be possible to influence the course of the disease, stopping death and turning on differentiation.
4. Transition of the cells to a senescent state allows maintaining barrier properties of the epidermis. However, the mechanisms of activation of this transition are apparently different. Are there really two pathways (p16- and p21-dependent) of senescence? Does the composition of SASP differ in different senescence pathways? Can drugs affect the composition of SASP? Is it necessary to block transition of the cells to a senescent state in the intact epidermis? Answers to these questions would help in selecting therapy using senolytics and senomorphics.

Abbreviations

ER	endoplasmic reticulum
RCD	regulated cell death
SASP	senescence-associated secretory phenotype
SB	stratum basale (basal layer)
SC	stratum corneum (cornified layer)
SCd	stratum disjunctum (outer cornified layer)
SG	stratum granulosum (granular layer)

SS stratum spinosum (spinous layer)
UV ultraviolet radiation

Contributions

O. P. Kisurina-Evgenieva – description of senescence and polyploidization mechanisms, text editing, preparation of illustrations; M. S. Vildanova – description of differentiation and corneoptosis mechanisms, preparation of illustrations; M. A. Savitskaya – description of cell death mechanisms; I. I. Zakharov – description of polyploidization and ER stress mechanisms, text editing; E. A. Vorotelyak – discussion and text editing.

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Ethics approval and consent to participate

This work does not contain any studies involving human and animal subjects.

Conflict of interest

The authors of this work declare that they have no conflicts of interest.

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