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Skin aging, gene expression and calcium

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ABSTRACT

The human epidermis provides a very effective barrier function against chemical, physical and microbial insults from the environment. This is only possible as the epidermis renews itself constantly. Stem cells located at the basal lamina which forms the dermoepidermal junction provide an almost inexhaustible source of keratinocytes which differentiate and die during their journey to the surface where they are shed off as scales. Despite the continuous renewal of the epidermis it nevertheless succumbs to aging as the turnover rate of the keratinocytes is slowing down dramatically. Aging is associated with such hallmarks as thinning of the epidermis, elastosis, loss of melanocytes associated with an increased paleness and lucency of the skin and a decreased barrier function. As the differentiation of keratinocytes is strictly calcium dependent, calcium also plays an important role in the aging epidermis.

Just recently it was shown that the epidermal calcium gradient in the skin that facilitates the proliferation of keratinocytes in the *stratum basale* and enables differentiation in the *stratum granulosum* is lost in the process of skin aging. In the course of this review we try to explain how this calcium gradient is built up on the one hand and is lost during aging on the other hand. How this disturbed calcium homeostasis is affecting the gene expression in aged skin and is leading to dramatic changes in the composition of the cornified envelope will also be discussed. This loss of the epidermal calcium gradient is not only specific for skin aging but can also be found in skin diseases such as Darier disease, Hailey–Hailey disease, psoriasis and atopic dermatitis, which might be very helpful to get a deeper insight in skin aging.

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1. Introduction

The skin is the largest organ of the human body covering about 1.8 m^2 in an average adult and is confronted with harsher conditions than any other organ. Although skin is incredibly durable and has an enormous regenerative capacity eventually it cannot escape aging. The epidermis as well as the dermis are becoming thinner and the dermoepidermal junction flattens. Whereas the predominant feature of aged dermis is the reduction and fragmentation of the extracellular collagen matrix, in the epidermis the turnover rate of the keratinocytes slows down considerably and the protein composition of the cornified envelope responsible for the barrier function changes dramatically (Rinnerthaler et al., 2013). In this review we are focusing on changes in the epidermis during aging, for the dermis we refer to other reviews (Farage et al., 2013; Makrantonaki and Zouboulis, 2007; Naylor et al., 2011).

At the dermoepidermal junction the epidermal stem cells reside and as cells move outwards from this compartment cell divisions stop and the keratinocytes start to differentiate. For this differentiation process calcium is of utmost importance.

2. Keratinocyte differentiation and calcium

Already in 1980 it was shown that a concentration of 1.44 mM calcium chloride is sufficient to drive mouse keratinocytes into differentiation. Two hours after addition of calcium salts desmosomes start to form. After 36 h also the DNA synthesis stops completely, the keratinocytes stratify in a timeframe of 1–2 days into up to 6 cell layers and they are completely differentiated after 3–4 days (Hennings and Holbrook, 1983; Hennings et al., 1980). An increase in the calcium level also leads to a binding of E-cadherin on one cell to E-cadherin on a neighboring cell and also induces interactions with intracellular proteins such as β-,α- and p120 catenine and the actin cytoskeleton which are important contributions to adherens junctions (Tu and Bikle, 2013; Wheelock and Johnson, 2003).

In contrast to this a reduction of calcium to a concentration of 0.1 mM is still sufficient for keratin synthesis, the cells are still competent to divide

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and grow as a monolayer, but this concentration is not leading to a stratification of the cells (Hennings and Holbrook, 1983; Hennings et al., 1980). But calcium is not the sole force for cell differentiation in the skin and its role in this process has been overestimated for a long time. A stronger influence on the differentiation capacity of human keratinocytes is exerted by cell density (Poumay and Coquette, 2007; Wille et al., 1984). It was shown that the colony forming efficiency of human keratinocytes is nearly independent of high calcium concentrations, but is affecting colony size (Wille et al., 1984). For example, two early markers of keratinocyte differentiation, keratin 1 and 10, are not expressed after addition of calcium, but are expressed at confluency (Drozdoff and Pledger, 1993; Poumay and Pittelkow, 1995). Interestingly cells are able to proliferate at high salt concentrations ($\geq$1.8 mM calcium), and only if confluency is reached the cell cycle inhibitors $p21^{WAF1}$ and $p27^{KIP1}$ are upregulated, c-Myc is down-regulated and Notch1 is activated. All these calcium-independent steps are necessary to cease cell division (Kolly et al., 2005).

Besides the formation of cell–cell contacts (e.g. desmosomes and desmosomal plaques with associated tonofilaments) (Hennings and Holbrook, 1983), also the stabilization of adhesion molecules (Demlehner et al., 1995; Kolly et al., 2005) and a morphological change from angular to flat and polygonal (Kolly et al., 2005), as well as the formation of the cornified envelope is mainly driven by calcium (Kasturi et al., 1993).

2.1. The calcium dependence of the cornified envelope formation

Apart from being the largest organ of the human body, the skin is also one of the most active tissues in respect to regeneration. Almost every 60 days the epidermis renews itself completely, replacing more than 80 billion keratinocytes in the body of an average adult. This self-renewal is continuous and starts at the basal layer of the epidermis. This so called *stratum basale* contains the stem cell population of keratinocytes producing the transit amplifying cells. These are constantly dividing and undergo cycles of differentiation accompanied by step-by-step movements to the outside surface of the epidermis. The outermost layer of the epidermis is called *stratum corneum* and consists exclusively of corneocytes, terminally differentiated, dead keratinocytes. The corneocytes are constantly scaling off (sometimes this layer is also called *stratum disjunctum*) and in this way the human body is losing 1.5 g of epidermis every day. This differentiation of keratinocytes along their way through the different layers of the epidermis to the surface, ultimately resulting in the formation of corneoctyes, is nothing else but a type of programmed cell death. In contrast to apoptosis though, which acts very fast and depends on the presence of preformed proteins (Bax, procaspases, etc.) that have to be activated, the cornification is a very slow and sequentially regulated process, requiring the synthesis of various proteins, their modification and finally their cross-linking (Candi et al., 2009, 2005).

The cornification process is initiated in the *stratum spinosum* with the expression of the proteins involucrin (Watt and Green, 1981), periplakin (Ruhrberg et al., 1997) and envoplakin (Ruhrberg et al., 1996). Especially the expression of invoulcrin is strictly calcium dependent. The calcium responsiveness of involucrin is based on the transcription factor AP1 as well as on the protein kinase C isoform delta (PKCdelta) (Deucher et al., 2002). In an initial step, the two members of the plakin family (periplakin and envoplakin) form a complex with involucrin and are attached to the inner surface of the plasma membrane (DiColandrea et al., 2000), forming a scaffold on which the envelope assembles (Sevilla et al., 2007). The recruitment as well as efficient binding of periplakin and envoplakin to the phospholipid bilayer requires the presence of calcium (Kalinin et al., 2004). All three proteins (envoplakin, involucrin and periplakin) become cross-linked in a Ca^{2+}-dependant manner, via the activity of the transglutaminase 1 enzyme by forming Nε-(γ glutamyl) lysine (isopeptide) bonds (LaCelle et al., 1998; Marekov and Steinert, 1998). This insoluble monolayer consisting of periplakin, involucrin and envoplakin is tightly attached to the cytoskeleton through the activity of the adaptor protein kazrin that is forming a bridge between desmoplakin and periplakin at desmosomes (Groot et al., 2004). Incubation of keratinocytes in a high Ca^{2+}-medium leads to a two-fold increase in expression levels after 24 h and to a clear co-localization of kazrin with desmoplakin at the cell border after 6 h. A combination of both kazrin overexpression and administration of Ca^{2+} leads to distinct changes in cell shape (Sevilla et al., 2008).

The continuing formation of the cornified envelope requires the production of so called 'lamellar bodies' in the *stratum spinosum* and *stratum granulosum*. These secretory, acidic branched tubular granules are formed by the trans-Golgi-network (Chapman and Walsh, 1989; Grayson et al., 1985) and primarily contain a multitude of different lipids, such as glucosylceramides and sphingomyeline (Raymond et al., 2008), but also a large variety of lipid-processing enzymes (Madison et al., 1998), antimicrobial peptides such as cathelicidin and beta-defensin (Braff et al., 2005; Oren et al., 2003), proteases as well as protease inhibitors (Galliano et al., 2006) and the structural protein corneodesmosin (Raymond et al., 2008; Serre et al., 1991). Corneodesmosin for example is a secreted glycoprotein found at corneodesmosomes and is involved in the corneocyte cohesion. The adhesive properties of this protein are achieved by its glycine- and serine-rich amino-terminal domain and are strictly calcium dependent (Jonca et al., 2002).

The secretion of the contents of the lamellar bodies is primarily responsible for the water-repellent as well as anti-microbial features of the skin. The exocytosis of the lamellar bodies and their fusion with the plasma membrane leads to a replacement of the phospholipid bilayer with ω-OH-ceramides that are in a further step cross-linked to the protein scaffold with the help of the already mentioned transglutaminase 1 (Kalinin et al., 2001). It has been demonstrated that the exocytosis of lamellar bodies is preceded by an influx of calcium ions into keratinocytes (Denda et al., 2003a).

The main component of the CE though is loricrin. This protein accounts for more than 80% of the whole cornified envelope's protein mass and is expressed in the *stratum granulosum* (Kalinin et al., 2001). A prerequisite for the synthesis of loricrin is a calcium concentration of above 0.1 mM. This protein shows a very low water solubility, and is therefore clustered into granules directly after synthesis (Ishida-Yamamoto et al., 1996). In the process of the formation of the cornified envelope loricrin is cross-linked to itself and to members of the SPRR (small proline rich repeat) family. This multigene family consists of 15 members in humans that are clustered in four subgroups: SPRR1 (two members), SPRR2 (11 members), SPRR3 and SPRR4 (one member each) (Eckert et al., 2005). Our own unpublished data clearly indicate that the addition of calcium to primary human keratinocytes dramatically increases the expression of most of the SPRRs. Because of their high solubility the SPRRs have a function as bridges between proteins and most probably increase the solubility of loricrin (Steinert and Marekov, 1999). They are also cross-linked via the already mentioned Nε-(γ glutamyl) lysine (isopeptide) bonds. The responsible enzymes are the calcium dependent-transglutaminases 1 and 3 (Ahvazi et al., 2003; Eckert et al., 2005). In a final step these loricrin-SPRR clusters are transported to the cell membrane and are then attached to the periplakin–involucrin–evoplakin scaffold (Kalinin et al., 2001). There is also the necessity of a multitude of further proteins for the formation of or cross-linking to the CE. One of these proteins is filaggrin. Similar to loricrin, a concentration of at least 0.15 mM calcium is needed for an efficient transcription (Hohl et al., 1991). The N-terminal part of the protein (S100 domain) was also described as a calcium binding domain (Markova et al., 1993). After proteolytic cleavage of a precursor, filaggrin is known to bundle keratins, primarily the keratins 1, 2e and 10 into macrofibrills. This bundling of keratins results in the typical flattened shape of corneocytes (Proksch et al., 2008). A calcium signal also promotes the bundling of keratins into tonofilaments (Whitfield, 1995). In addition, filaggrin is also cross-linked to the matrix of the cornified envelope (Steinert and Marekov, 1995). Even two protease inhibitors,

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