SKIN BARRIER: CLINICAL IMPLICATIONS AND THERAPEUTIC RELEVANCE

ESSAY

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List of Abbreviations

α ····· Alpha

ABCA1 ····· Adenosine triphosphate binding cassette transporter 1

AD ····· Atopic dermatitis

AMPs····· Antimicrobial peptides

β ····· Beta

CHILD ····· Congenital Hemidysplasia with Ichthyosiform Erythroderma and Limb Defects

CLM····· Confocal laser microscopy

CO_2 ····· Carbon dioxide

CSO_4 ····· Cholesterol sulfate

DM····· Diabetes mellitus

EDC ····· Epidermal differentiation complex

FAS ····· Fatty acid synthase

FLG····· Filagrin gene

γ ····· Gamma

hBD····· Human β-defensins

HIV ····· Human immunodeficiency virus

HMG-CoA ····· 3-hydoxy-3-methyl-glutary-coenzyme A

IGF- 1 ····· Insulin-like growth factor I

IL····· Interleukin

INF····· Interferon

KLKs …… Kallikrein (s)

LBs…… Lamellar bodies

LCE…… Late cornified envelope

LXRs …… Liver X receptors

MHC…… Major histocompatibility complex

NGF …… Nerve growth factor

NMF…… Natural moisturizing factor

OCT …… Optical coherence tomography

OTC …… Over-the-counter

PAMPs…… Pathogen-associated molecular patterns

PAR2 …… Proteinase-activated receptor 2

PCA…… pyrrolidone carboxylic acid

PPARs…… Peroxisome proliferator-activated receptors

PRRs …… Pattern recognition receptors

PSORS1 …… Psoriasis susceptibility locus 1

S. aureus …… Staphylococcus aureus

SC…… Stratum corneum

SCD1…… Stearoyl-CoA desaturase 1

SP …… Serine protease

SPT …… Serine palmitoyl transferase

STS …… Steroid sulfatase

TCI…… Topical calcineurin inhibitors

TCS…… Topical corticosteroids

TEWL …… Transepidermal water loss

TG…… Transglumatinase

TH…… T-helper

TLRs…… Toll-like receptors

TNF-α …… Tumor necrosis factor alpha

TRP …… Transient receptor potential

UCA …… Urocanic acid

UV …… Ultraviolet

VEGF…… Vascular endothelial growth factor

XLI…… X-linked ichthyosis

Introduction and aim of the work

The skin is the primary interface between the body and the external environment, being a vital organ for life. Among its many functions, the role as a defensive barrier is one of the most important functions ***(Ramos-e-Silva and Jacques, 2012).*** Although the whole skin structure actively participates in the host defense, the epidermis is important in preventing loss of water and other components of the body to the environment (inside–outside barrier) and in protecting the body from a variety of environmental insults (outside–inside barrier) ***(Baroni et al., 2012).***

The epidermis protects the skin from potentially hazardous environmental threats, providing physical, chemical and immunologic barriers ***(Baroni et al., 2012).***

The skin has several facets that function as parts of the nonspecific immune response. These key elements include physical and chemical barriers and recruitment and activation of various leukocytes ***(Niyonsaba et al., 2009).*** Besides, the skin immune system is equipped with a variety of sophisticated tools that lead to an efficient defence system against various infectious challenges. The immune system has receptors that recognize molecules present on pathogenic microorganisms. These receptors function to promote the innate immune response to microorganism exposure that leads to a proinflammatory response ***(Jouault et al., 2009).***

The assessment of the epidermal barrier provides information on epidermal permeability barrier status under normal, experimentally perturbed, or diseased conditions ***(Fluhr et al., 2006).***

The traditional invasive method of skin biopsy to investigate skin barrier function contains limitations as well as advantages. Its invasive

nature inhibits the ability of investigators to repeat their measurements and perform frequent comparisons; furthermore, the results of in vitro and in vivo experiments using a skin biopsy specimen do not always correlate ***(Sotoodian and Maibach 2012).***

Today, different non-invasive approaches are used to monitor the skin barrier physical properties in vivo. Novel methods such as in vivo confocal laser microscopy offer the possibility for precise and detailed characterization of the skin barrier ***(Darlenski and Fluhr, 2012).***

It becomes evident now that understanding all aspects of skin barrier regulation and function has far-reaching implications in our everyday practice, on our ability to understand the normal physiology of the skin and of the pathophysiology of various skin diseases. Moreover, this provides an improved insight into the interaction of the skin with the environment, with skin care products, and with topical treatments ***(Wolf and Parish 2012).***

AIM OF THE WORK

The aim of this essay is to provide:

- An update on the biology of skin barrier and its clinical implications.
- An update on the novel bioengineering techniques to assess and restore a defective barrier.

Structure and function

The skin is a continuously self-renewing organ that covers the surface of the body and separates it from the outside world with which it connects in a dynamic way. It provides protection against external agents such as mechanical and chemical insults, heat, infections, water, and electromagnetic radiation ***(Baroni et al., 2012).***

The skin is divided into two main structural compartments: the epidermis or epithelial component coating on the surface, and the dermis or connective tissue component for nutrition. Both skin compartments cooperate in the formation of a highly specialized matrix structure, the basement membrane which physically separates the two compartments, providing a stabilizing as well as dynamic interface ***(Breitkreutz et al., 2009).***

Although the whole skin structure actively participates in the host defense, the epidermis is important in preventing loss of water and other components of the body to the environment (inside–outside barrier) and in protecting the body from a variety of environmental insults (outside–inside barrier) ***(Baroni et al., 2012).***

1) The epidermis and the main-line epidermal barrier:

The epidermis is a continually renewing epithelium, usually subdivided into several layers or strata, starting with the basal layer (or stratum basale) just above the dermis and proceeding upward through the spinous and granular layers to the top layer, the stratum corneum (SC). Its main function is to protect the skin from potentially hazardous environmental threats, providing physical, chemical and immunologic barriers ***(Randall and Visscher, 2006).***

The physical barrier mainly consists of the SC, although the cell–cell junctions and associated cytoskeletal proteins in the lower layers provide further important components ***(Proksch et al., 2008).***

The chemical barrier consists of lipids, acids and hydrolytic enzymes. The immunologic barrier is composed of humoral and cellular constituents of the immune system ***(Baroni et al., 2012).***

i) The physical and chemical barrier:

The predominant cell type of the epidermis is the keratinocyte, which is nucleated and viable from the basal layer to the granular layer ***(Randall and Visscher, 2006).***

The final steps in keratinocyte differentiation are associated with profound changes in their structure, resulting in a transformation into flat and anucleated squamous cells of the SC called corneocytes. These cells are surrounded by a cell envelope composed of cornified envelope proteins formed on the inner surface of the corneocyte plasma membrane ***(Nishifuji and Yoon, 2013).*** These proteins comprised predominantly of loricrin (70%), and other proteins including involucrin, cornifin, elafin, type II keratins, filaggrin, desmoglein, envoplakin, and small proline-rich proteins. On the surface of the corneocytes, calcium-dependent transglutaminases (TGs) crosslink the proteins of the cornified cell envelope developing highly insoluble gamma glutamyl-lysine bonds. **(*Fluhr and Darlenski, 2009).***

On the exterior surface of the cornified envelope surrounding each corneocyte, a covalently bound lipid envelope (figure 1) ***(Baroni et al., 2012).***

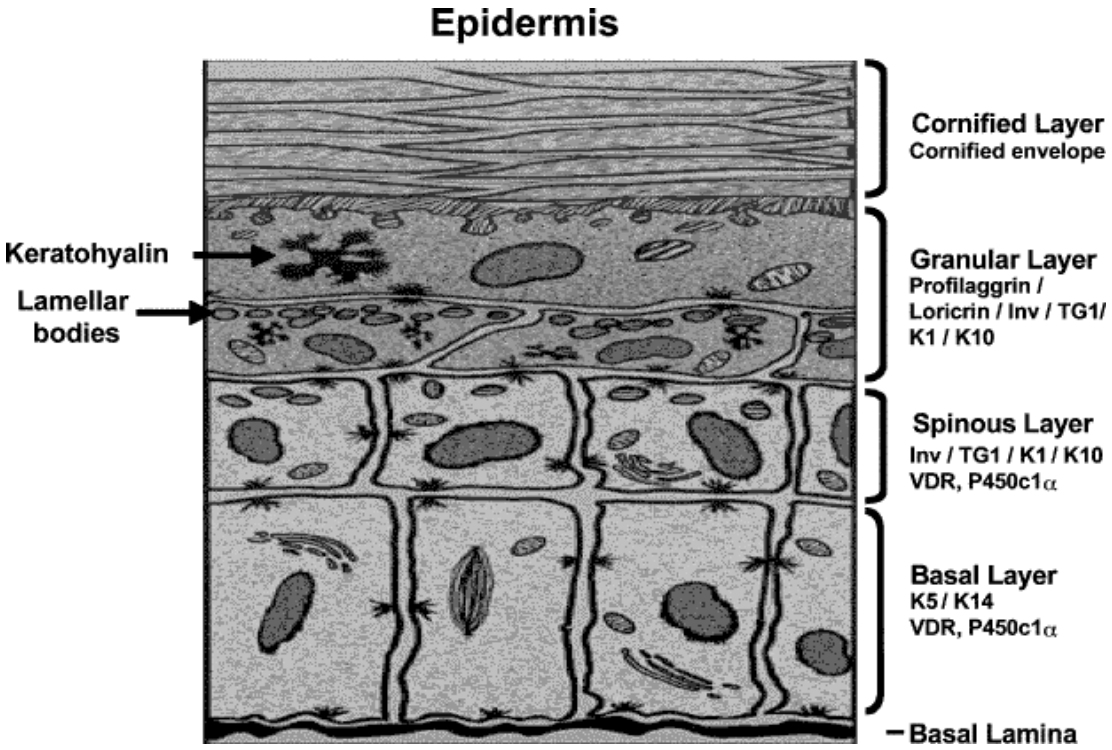

Fig.1: Diagramatic illustration of different epidermal strata. K1/K10; keratins 1 and 10, K5/K14; keratins 5 and 14, TG1; transglumatinase 1, Inv; involuricin ***(Bikle et al., 2004).***

The SC serves as the principal barrier against the percutaneous penetration of chemicals and microbes and is capable of withstanding mechanical forces ***(Madison, 2003).*** For several years, there was a belief that the SC is essentially a dead layer devoid of any functional activity. It was further entrenched in mainstream thinking by its description as "basketweave hyperkeratosis" when viewed histologically after routine processing as illustrated in figure (2) ***(Del Rosso and Levin, 2011).***

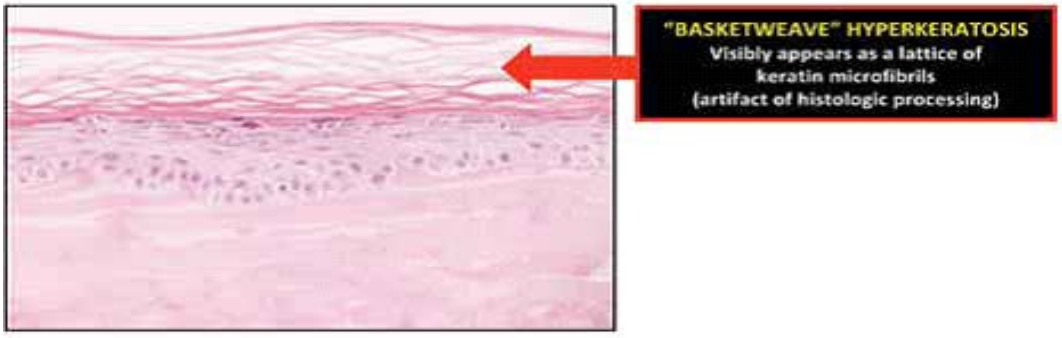

Fig.2: The basketweave appearance of the SC ***(Del Rosso and Levin, 2011).***