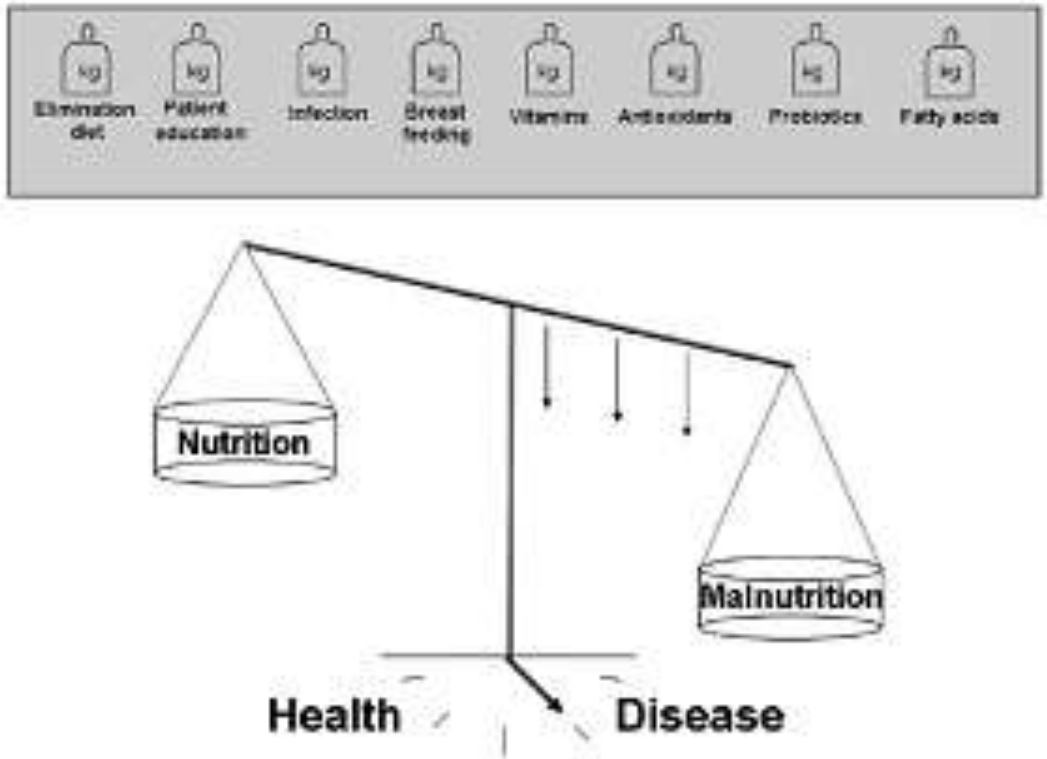


FIG 1. The balance between nutrition and malnutrition and the factors that preponderate on the outcome of health and disease in this interplay are shown.

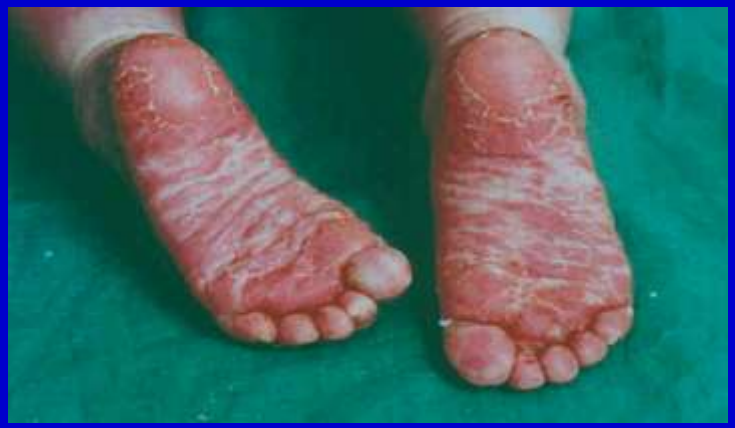
Balneoterapie – imunomodulační nástroj

Doplňkové léčebné možnosti
(as.MUDr.Š.Čapková)

- **Lázeňská léčba:** klimaticky vhodná oblast, koupele, léčba dermatologická

- **Přímořská léčba:** fototerapie, vliv podnebí, sůl na kůži

- **Klimatická léčba (hory):** nízké množství alergenů, chladnější klima



Balneoterapie – imunomodulační nástroj

- ✓ UV terapie
- ✓ modulace nespecifické imunity
- ✓ změna prostředí
- ✓ stres

Balneoterapie – imunomodulační nástroj

✓ UV terapie

Tabelle 106.1. Einteilung der optischen Strahlung

Wellenbereich	Abkürzung	Wellenlänge[a]
Kurzwelliges UV	UVC	200–280 nm
Mittelwelliges UV	UVB	280–320 nm
Langwelliges UV	UVA	320–400 nm
	UVA2	320–340 nm
	UVA1	340–400 nm
Sichtbares Licht	SL	400–800 nm
Kurzwelliges Infrarot	IR-A	800–3000 nm
Mittelwelliges Infrarot	IR-B	3–10 µm
Langwelliges Infrarot	IR-C	10 µm–1 mm

[a] International in den Naturwissenschaften gebräuchliche Einteilung. Daneben bestehen in nationalen Richtlinien geringfügig abweichende Definitionen (wie nach DIN: UVB: 290–315 nm, UVA: 315–380 nm)

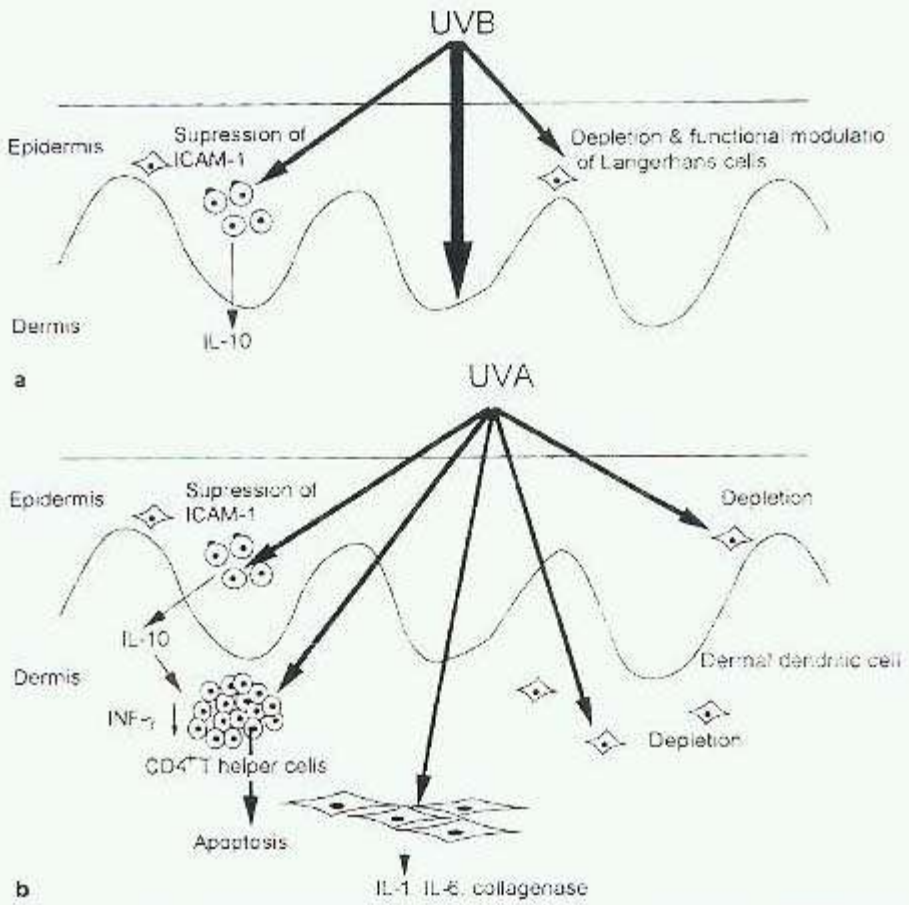


Fig. 1a, b. Scheme of immunomodulatory effects induced by UVB- [A] or UVA(1)-[B] photo(chemo)therapy. *ICAM-1*, intercellular adhesion molecule-1; *IFN-γ*, interferon-γ; *IL-10*, interleukin-10

Table 1. Subsets of natural and induced regulatory T cells[1]

Treg subset	Regulatory mechanisms	Transcription factor expressed	Target cells	Function
$CD4^+CD25^+$ Tregs	Cell contact-dependent, cytokines (IL-10?[2])	Foxp3	T cells, APCs	Suppression of autoimmunity; inhibition of allograft rejection and of immune responses induced by microbial infection; mediation of UV-induced immunosuppression
$CD4^+CD25^-$ Tregs	Mostly mediated by cytokines	Foxp3 (?[2])	T/B cells, APCs	Suppression of autoimmunity
Tr1 cells	Mediated by IL-10	Foxp3 (?[2])	T cells	Suppression of autoimmunity
Th3 cells	Mediated by TGF-β	?[2]	T cells	Suppression of autoimmunity
NKTregs	IL-4, IL-10, TGF-β, cytotoxicity	?[2]	T cells, APCs, tumor cells	Elimination of tumors and pathogens; suppression of autoimmunity; mediation of UV-induced suppression of protective tumor immunity
$CD8^+$ Tregs	Cell contact-dependent, cytotoxicity, cytokines (?[2])	Foxp3 (?[2])	T cells	Suppression of autoimmunity; regulation of peripheral TCR repertoire
$CD8^+CD28^-$ Tregs	Induction of ILT3/ILT4 in DCs	Foxp3 (?[2])	DCs/APCs	Regulation of autoimmunity (?[b])

[1]Subsets have been detected in humans and rodents. [2]Issue uncertain, not yet clear or not yet investigated. Abbreviations: APC, antigen-presenting cell; DC, dendritic cell; ILT, immunoglobulin transcript; NKTreg, regulatory cell of natural killer T cell phenotype; Th3, T helper type 3; Tr1 cell, type 1 regulatory T cell; Treg, regulatory T cell.

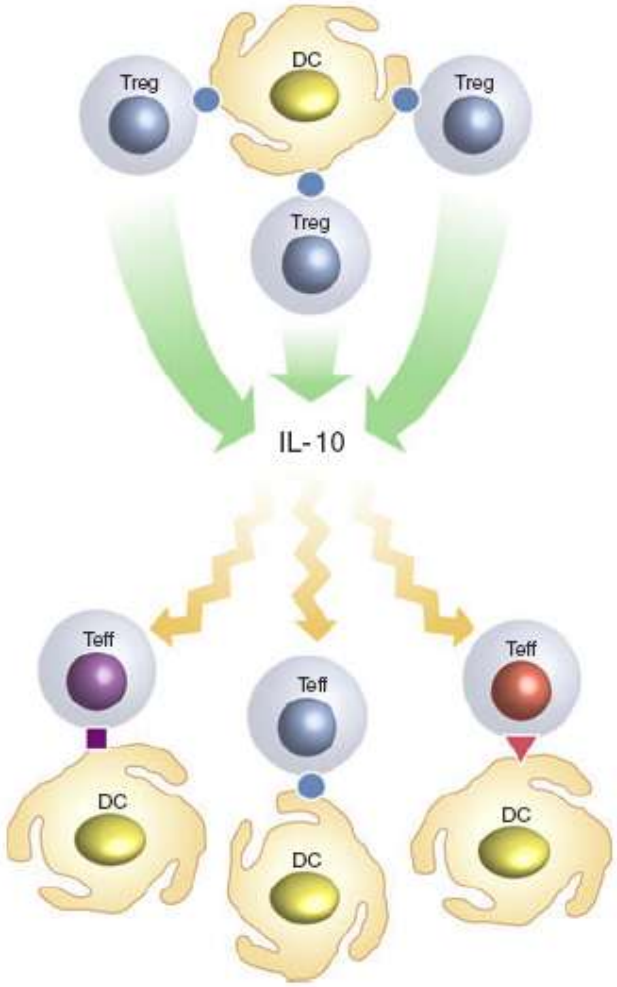
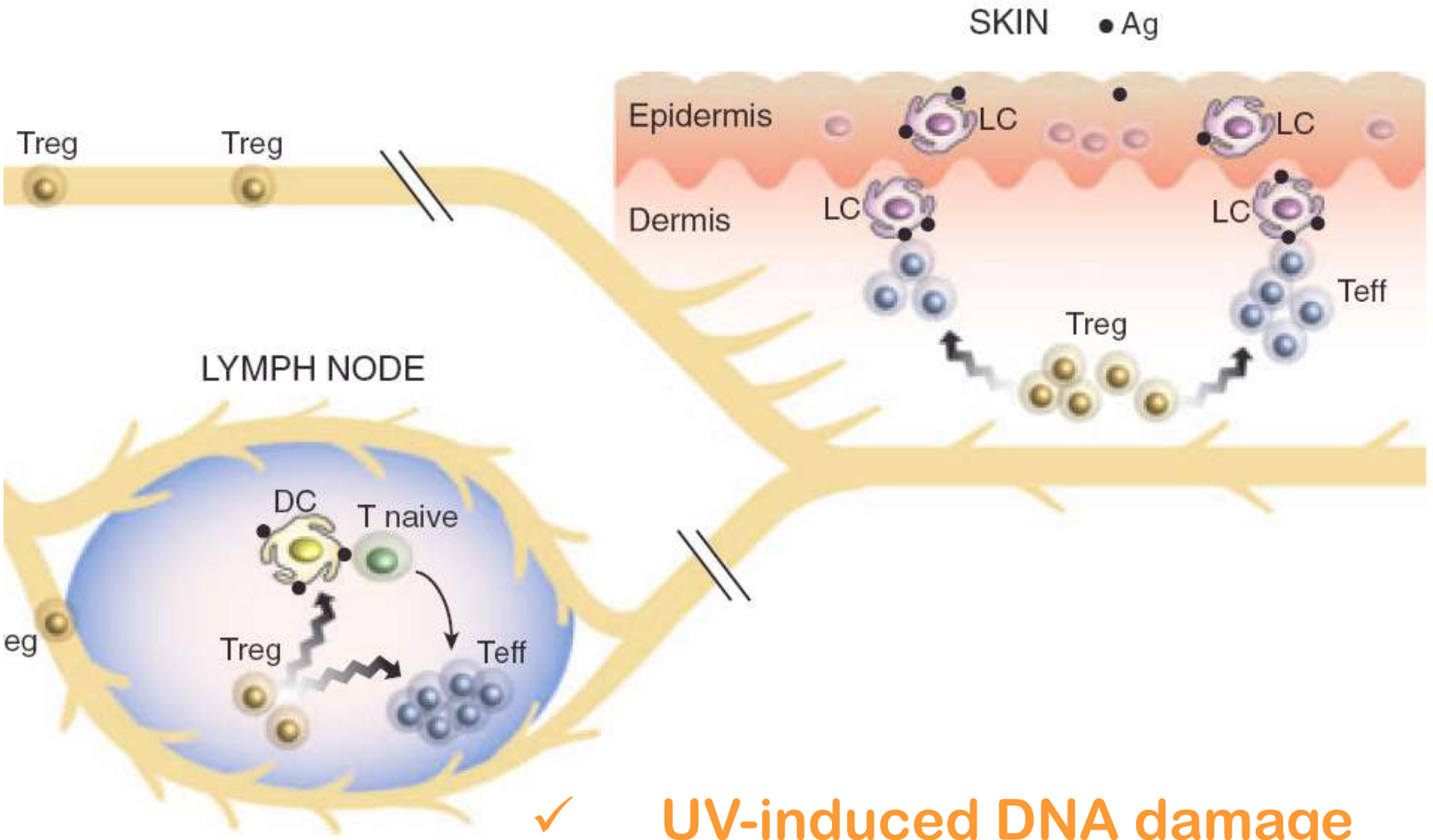


Figure 2. Mechanism of bystander suppression. Tregs that are activated by DCs in an antigen-specific fashion release IL-10. Once released, IL-10 inhibits immune reactions not only against the initial antigen (●) but also against other antigens (▼, ■) in a nonspecific fashion.



- ✓ **UV-induced DNA damage**
- ✓ **IL-10 Treg**
- ✓ **IL-12 reduces LC-DNA damage**

Solar-Simulated Ultraviolet Radiation Induces Abnormal Maturation and Defective Chemotaxis of Dendritic Cells

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*Servicio de Inmunología and †Servicio de Dermatología, Hospital de la Princesa, Universidad Autónoma de Madrid, Madrid, Spain; ‡Industria Farmacéutica Cantabria, Madrid, Spain; §Wellman Laboratories of Photomedicine, Harvard Medical School, Boston, Massachusetts, USA

Exposure to ultraviolet (UV) light induces immunosuppression. Different evidences indicate that this phenomenon is mainly a consequence of the effect of UV light on skin dendritic cells (DC). To investigate the cellular and molecular basis of this type of immunosuppression, we assessed *in vitro* the effect of solar-simulated UV radiation on the phenotypic and functional characteristics of human monocyte-derived DC and Langerhans-like DC. UV radiation induced a decreased expression of molecules involved in antigen capture as DC-SIGN and the mannose receptor. This effect was accompanied by a diminished endocytic capacity, an enhanced expression of molecules involved in antigen presentation such as major histocompatibility complex-II and CD86, and a significant increase in their capability to stimulate T cells. Furthermore, irradiated DC failed to acquire a full mature phenotype upon treatment with lipopolysaccharide. On the other hand, solar-simulated radiation induced the secretion of tumor necrosis factor-αand interleukin (IL)-10 by DC, but no IL-12. Interestingly, solar-simulated UV radiation also caused an altered migratory phenotype, with an increased expression of CXCR4, and a lack of induction of CCR7, thus correlating with a high chemotactic response to stromal cell-derived factor 1(SDF-1) (CXCL12), but not to secondary lymphoid tissue chemokine (SLC) (CCL21). These data indicate that solar-simulated UV radiation induces a defective maturation and an anomalous migratory phenotype of DC.

Key words: chemotaxis/costimulation/cytokines/dendritic cells/human
J Invest Dermatol 125:334–342, 2005

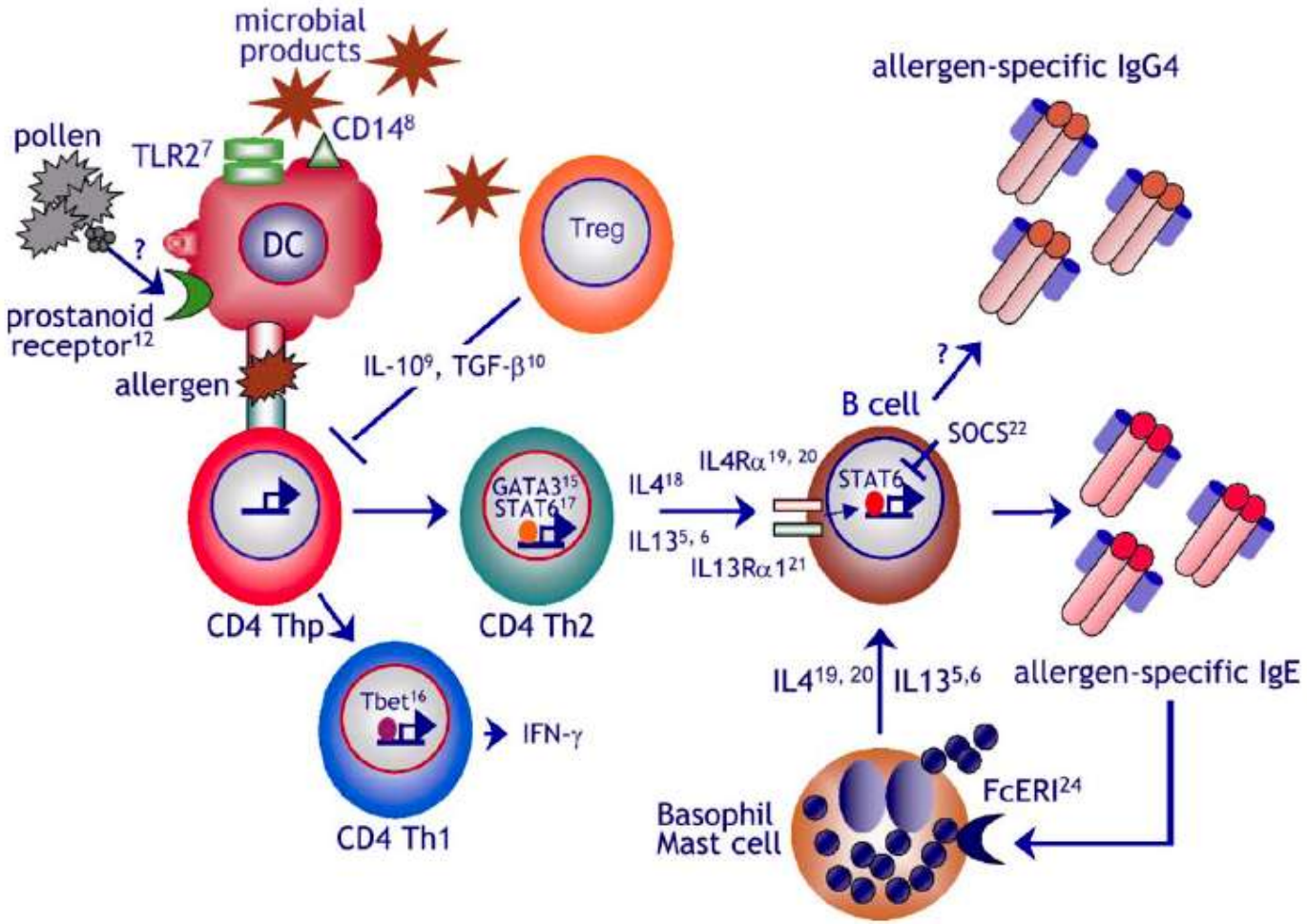


FIG 1. Gene-gene interactions and the pathogenesis of allergic inflammation: a working roadmap. Groups of interactions are color coded: the regulatory and sensing interfaces are in *red/orange*, T_H differentiation is in *blue/green*, and the effector phase is in shades of *brown*. See text for an in-depth discussion of individual pathways and genes. References are numbered as in the text.

Tabelle 106.5. Indikationen zur UVB-Phototherapie

Indikation	UVB-Breitband	UVB-311 nm
Psoriasis	+	++
Atopisches Ekzem	+	++
Pruritus, Prurigo	+	+
Parapsoriasis en plaques	+	+
Mycosis fungoides (Patch-Stadium)	+	+
Prophylaxe der polymorphen Lichtdermatose	+	++
Vitiligo	–	++
Pityriasis lichenoides	+	0
Lymphomatoide Papulose	+	0
Seborrhoisches Ekzem	+	+
HIV-assoziierte pruritische Eruptionen	+	0

+ empfehlenswert, ++ überlegen, – gering wirksam, *0* keine Erfahrungsberichte

Tabelle 106.8. Indikationen für UVA1-Phototherapie

Standardtherapie	Wissenschaftliche Erprobung
Atopisches Ekzem	Urticaria pigmentosa
Dyshidrosiformes Hand- und Fußekzem	Granuloma anulare
Morphea	Sarkoidose
	Lichen sclerosus et atrophicus
	Lichturtikaria
	Mycosis fungoides
	Psoriasis
	Pruritus
	Prurigo
	Akrale systemische Sklerodermie
	Akute und chronische Graft-versus-Host-Erkrankung

Tabelle 106.10. Häufigste Indikationen für Photochemotherapie

Diagnose	PUVA oral	PUVA-Vollbad	PUVA-Hand- und Fußbad
Psoriasis vulgaris	+	+	
Palmoplantare Psoriasis			+
Atopisches Ekzem	+	+	
Dyshidrosiformes und hyperkeratotisches Hand- und Fußekzem			+
Parapsoriasis en plaques	+	+	
Mycosis fungoides	+	+[a]	
Lymphomatoide Papulose	+	+	
Morphea	+	+	
Akute und chronische (sklerodermiforme) Graft-versus-Host-Erkrankung	+	+	
Lichen ruber	+	+	+
Photodermatosen Polymorphe Lichtdermatose Lichturtikaria Chronische aktinische Dermatitis Hydroa vacciniformia Aktinische Prurigo	+		

[a] Gesicht muss von der Behandlung ausgespart bleiben, daher kann nicht die bei Mycosis fungoides meist notwendige Ganzkörpertherapie erfolgen

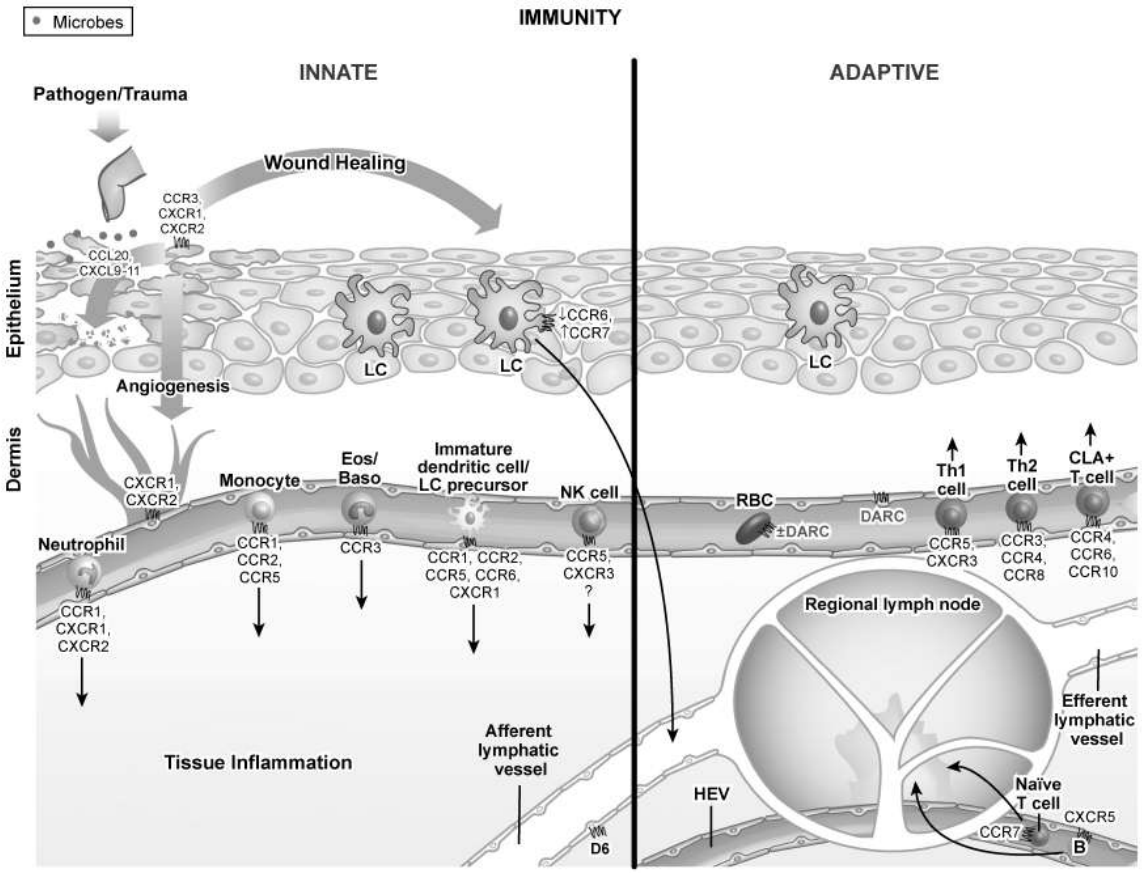
Tabelle 106.14. Risiken und Nebenwirkungen der Photo(chemo)therapie

	UVB	UVA/UVA1 <20 J/cm²	UVA1 >20 J/cm²	PUVA
Sonnenbrand und phototoxische Reaktion bei Überdosierung	++	–	–	++
Phototoxische Reaktion durch unbeabsichtigte Zufuhr eines Photosensibilisators	±	+	++	++
Konjunktivitis und Keratitis bei fehlendem Augenschutz	++	–	–	++
Provokation von Photodermatose (polymorphe Lichtdermatose)	+	+	++	±
UV-Lentigines	+	±	+	++
Lichtalterung der Haut	++	±	++	++
Präkanzerosen und spinozelluläres Karzinom	+	?	±	++
Melanome	?	?	?	?

++ hohes Risiko; + mäßiges Risiko; ± geringes Risiko; – aufgrund bekannter Wirkmechanismen nicht wahrscheinlich; ? prinzipiell möglich, aber keine Daten vorhanden

Balneoterapie – imunomodulační nástroj

✓ **modulace nespecifické imunity**



Humorální faktory v kožním imunitním systému

Antimikrobiální peptidy -defensiny, cathelicidiny,dermcidiny

Lysozym

Složky komplementového systému (C3,fB,fH; CD59 /DAF/, CD46 /MCP/, CD59; CR1, CR2)

Cytokiny (IL-1, TNF-α , … interferony, chemokiny…)

Imunoglobuliny (IgG, IgA vč. SIgA)

Fibrinolysiny

Produkty koagulační kaskády

Eikosanoidy a prostaglandiny

Neuropeptidy

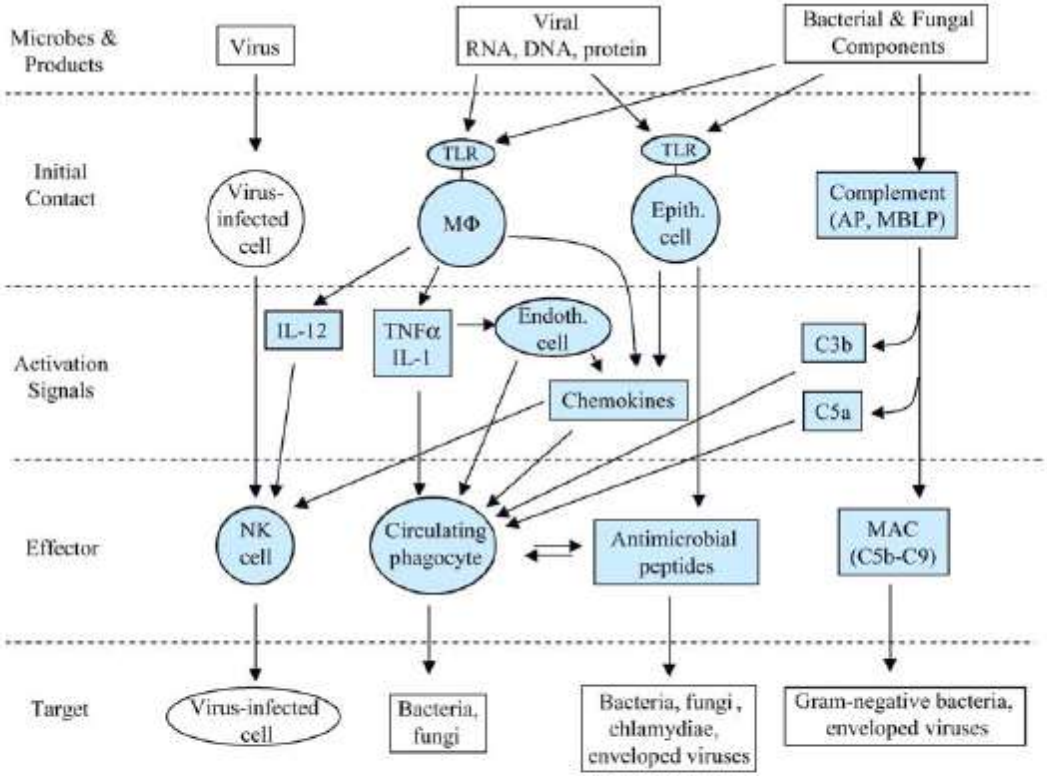


FIG 1. Innate immunity: responses to first contact. Diagrammed are important host responses to infection that are independent of specific cell-mediated immunity or antibodies. Initial contact between the host and microbes or their products results in a range of activating signals that mobilize both cellular and humoral effectors for attack on their respective microbial targets. Components of the host response are highlighted in blue. *MΦ*, Macrophages; *AP*, alternative pathway; *MBLP*, mannose-binding lectin pathway.

Stratum Corneum Defensive Functions: An Integrated View

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Most epidermal functions can be considered as protective, or more specifically, as defensive in nature. Yet, the term "barrier function" is often used synonymously with only one such defensive function, though arguably its most important, i.e., permeability barrier homeostasis. Regardless of their relative importance, these protective cutaneous functions largely reside in the stratum corneum (SC). In this review, I first explore the ways in which the multiple defensive functions of the SC are linked and interrelated, either by their shared localization or by common biochemical processes; how they are co-regulated in response to specific stressors; and how alterations in one defensive function impact other protective functions. Then, the structural and biochemical basis for these defensive functions is reviewed, including metabolic responses and signaling mechanisms of barrier homeostasis. Finally, the clinical consequences and therapeutic implications of this integrated perspective are provided.

Key words: barrier function/corneodesmosomes/cytokines/desquamation/hydration/lamellar bodies/pH/psychological stress/stratum corneum/lamellar body
J Invest Dermatol 125:183–200, 2005

Table I. Protective functions of mammalian stratum corneum

Function	Localization
Permeability barrier[a]	Extracellular
Cohesion (integrity) → desquamation[a]	Extracellular
Antimicrobial barrier (innate immunity)[a]	Extracellular
Mechanical (impact and shear resistance)	Corneocyte
Toxic chemical/antigen exclusion	Extracellular
Selective chemical absorption	Extracellular
Hydration	Corneocyte
UV barrier	Corneocyte
Initiation of inflammation (cytokine activation)[a]	Corneocyte
Psychosensory interface	Unknown
Thermal barrier	Unknown

[a]Regulated or thought to be activated by (SC) pH.

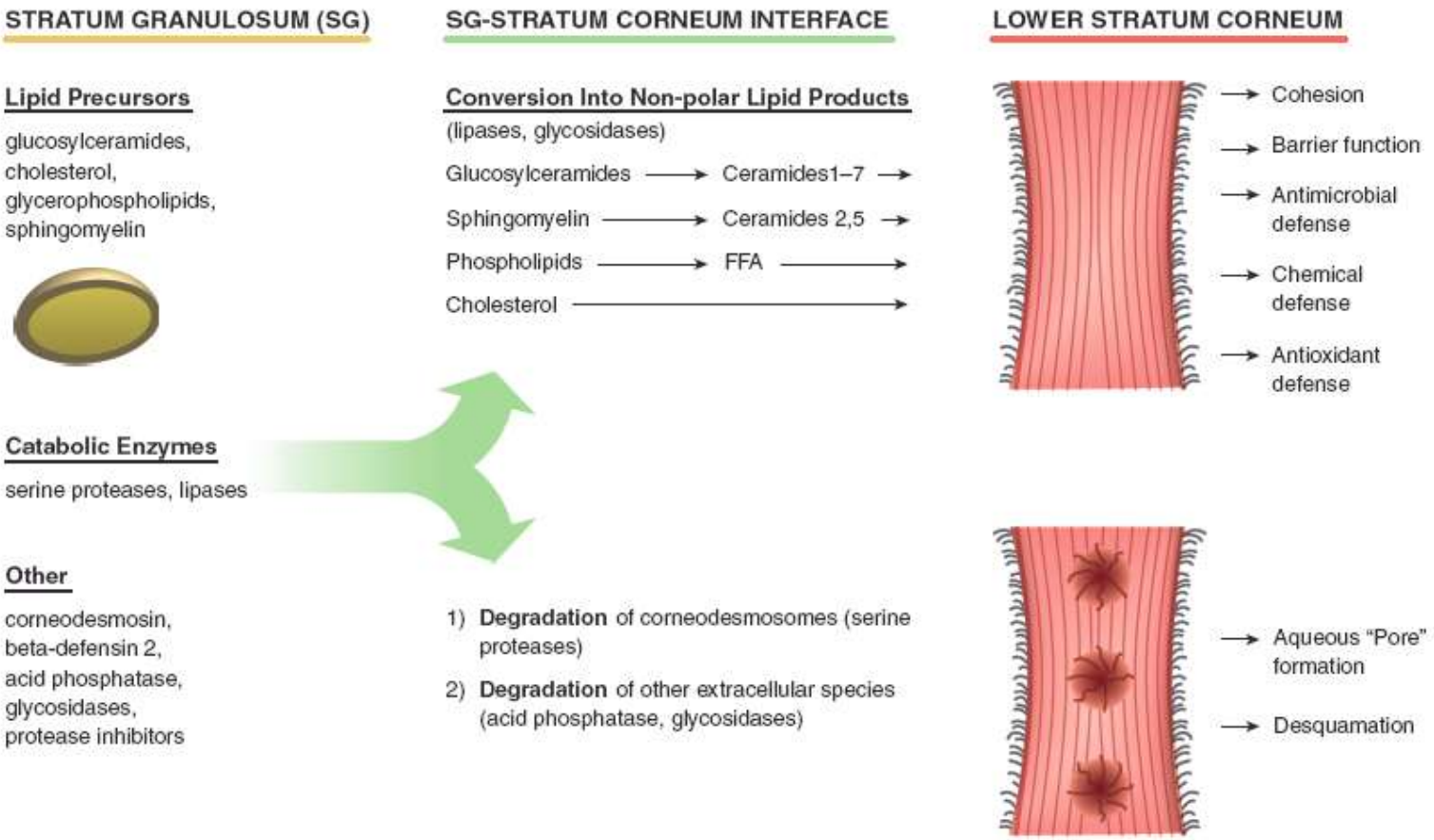


Figure 1
Lamellar body secretion dictates localization of multiple functions to extracellular compartment.

Hydration, ultraviolet (UV) filtration, and immunosuppression are linked through the histidase pathway In addition to resistance of the skin to *mechanical* or blunt *injury*, corneocytes ("bricks") generate filaggrin-derived peptides and their deiminated products, which, along with sebaceous gland-derived glycerol (Fluhr *et al*, 2003), regulate not only SC *hydration* but also several other downstream functions (Fig 2). Early in cornification, filaggrin, the predominant, histidine-enriched, basic protein in F-type keratohyalin granules, disperses around keratin filaments within the stratum compactum (Dale *et al*, 1997). At ambient humidities (<85% RH), i.e., above the stratum compactum, filaggrin is largely hydrolyzed by a still-uncharacterized, cytosolic protease into free amino acids, including histidine, glutamine (glutamic acid), and arginine (Scott and Harding, 1986; Harding *et al*, 2000). These amino acids, and their distal, deinminated products (urocanic acid, pyrrolidone carboxylic acid, and ornithine/citrulline/aspartic acid, respectively) comprise much of the osmotically active material that regulates SC hydration (Harding *et al*, 2000). Histidine is deiminated enzymatically to its acidic, polar, plurifunctional metabolite, trans-urocanic acid (tUCA), by the enzyme, histidine ammonia lyase (histidase) (Scott, 1981). As it acts as an *endogenous sunscreen*, tUCA is photoisomerized by UV-B to cUCA (De Simone *et al*, 2001), a potent *immunosuppressive* molecule, implicated in the pathogenesis of UV-induced skin cancers (Noonan and De cohesion by a common mechanism, i.e., suppression of epidermal lipid synthesis and LB production (Kao *et al*, 2003). Accordingly, not only the stress-induced barrier abnormality, but also the abnormality in SC integrity can be reversed (overridden) by a mixture of physiologic lipids, containing all three key SC species (i.e., ceramides, FFA, and cholesterol) (Kao *et al*, 2003).

Impact of pH on multiple defensive functions A second example of a common stressor that modulates multiple functions is SC pH. In fact, pH orchestrates at least three important SC defensive functions (Table I). Using a flat surface electrode, the pH of mammalian SC typically ranges from 4.5 to 5.0 in the outer SC, approaching neutrality in the lower SC (Ohman and Vahlquist, 1994). Recent studies, utilizing fluorescence-lifetime imaging (FLIM) combined with mutliphoton microscopy, show that SC pH is heterogeneously distributed, and that the pH gradient is non-linear (Behne *et al*, 2002, 2003). Most importantly, FLIM demonstrated that membrane domains even at the level of the stratum granulosum (SG)–SC interface are selectively acidified (Behne *et al*, 2002).

Although at least two endogenous, biochemical pathways regulate SC pH, the full array of functions that are impacted by each mechanism is still largely unclear. A third mechanism is the histidine-to-UCA pathway, which can account quantitatively for SC acidification (Krien and

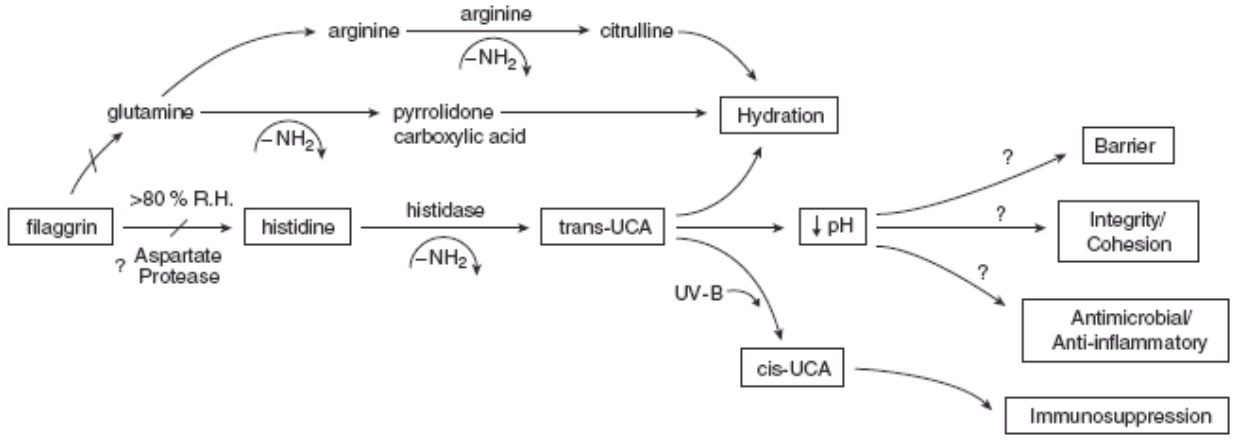


Figure 2
Functions potentially impacted by filaggrin metabolism in the stratum corneum.

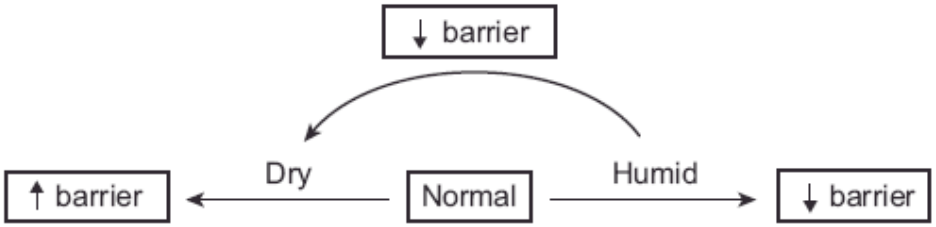


Figure 4
Changes in external humidity alter permeability barrier function.

Signals of Barrier Homeostasis

Transcriptional regulation of corneocyte protein expression by nuclear hormone receptor (NHR) ligands. Members of both the Class I and Class II family of NHR influence epidermal barrier formation, function, and development (Table II). At least three ligands (glucocorticoids, estrogens, and androgens) of the Class I family (receptors for the steroid hormones) regulate permeability barrier development in fetal skin, as well as barrier homeostasis in adult skin. In fetal skin both exogenous glucocorticoids and estrogens, either administered *in utero* or added directly to fetal skin explants in organ culture, accelerate the development of a mature permeability barrier, whereas in contrast, administration of androgens retards barrier ontogenesis (Hanley *et al*, 1996a, b, 1998). Although the impact of Class I ligands on barrier function in post-natal skin is less well understood, normal to supra-normal levels of androgens provoke an analogous decline in permeability barrier homeostasis in adult murine and human skin (Kao *et al*, 2001). Yet, an increase in endogenous glucocorticoids, induced by either psychological stress (Denda *et al*, 2000), or systemic administration of exogenous steroids (Kao *et al*, 2003), alters permeability barrier homeostasis and SC integrity/cohesion.

Table II. Cutaneous effects of class II NHR ligands

Receptor	Ligands/activators	Fetal barrier development	Adult barrier homeostasis	Anti-inflammatory
Classic				
RAR	All-trans-retinoic acid	None	Worse	Improves
T3R	Triodothyronine (T3)	Accelerates	?	?
D3R	$1,25(OH)_2$ vitamin D3	None	Worse	Improves
Liposensor				
PPARα	Leukotriene B4, fatty acids, fibrates	Accelerate	Accelerate	Improve
PPARγ	Prostaglandin J_2, troglitazone	None	None	Improve
PPARδ	Free fatty acids	None	Accelerate	Improve
LXR	Oxygenated sterols	Accelerate	Accelerate	Improve

NHR, nuclear hormone receptor; PPAR, peroxisome proliferator activator receptor; LXR, liver X receptor.

Table III. Protease–anti-protease reactions in stratum corneum

	Preferred substrate	Anti-proteases
Serine proteases		
SCTE	DSG1, pro-SCCE	LEKTI 1
SCCE	DSC1, CDSN	SKALP, SLPI, LEKTI 1
Cysteine proteases		
SCCP	DSC1, CDSN	Cystatin M/E, Cystatin α, SLPI
Aspartate proteases		
Cathepsin G	DSC1, CDSN	SLPI

SC, stratum corneum; SCTE, SC tryptic; SCCE, SC chymotryptic; SCCP, SC cysteine protease; DSG1, desmoglein 1; DSC1, desmocollin 1; CDSN, corneodesmosin; SLPI, secretory leukocyte protease inhibitor; SKALP, skin-derived antileukocyte proteinase.

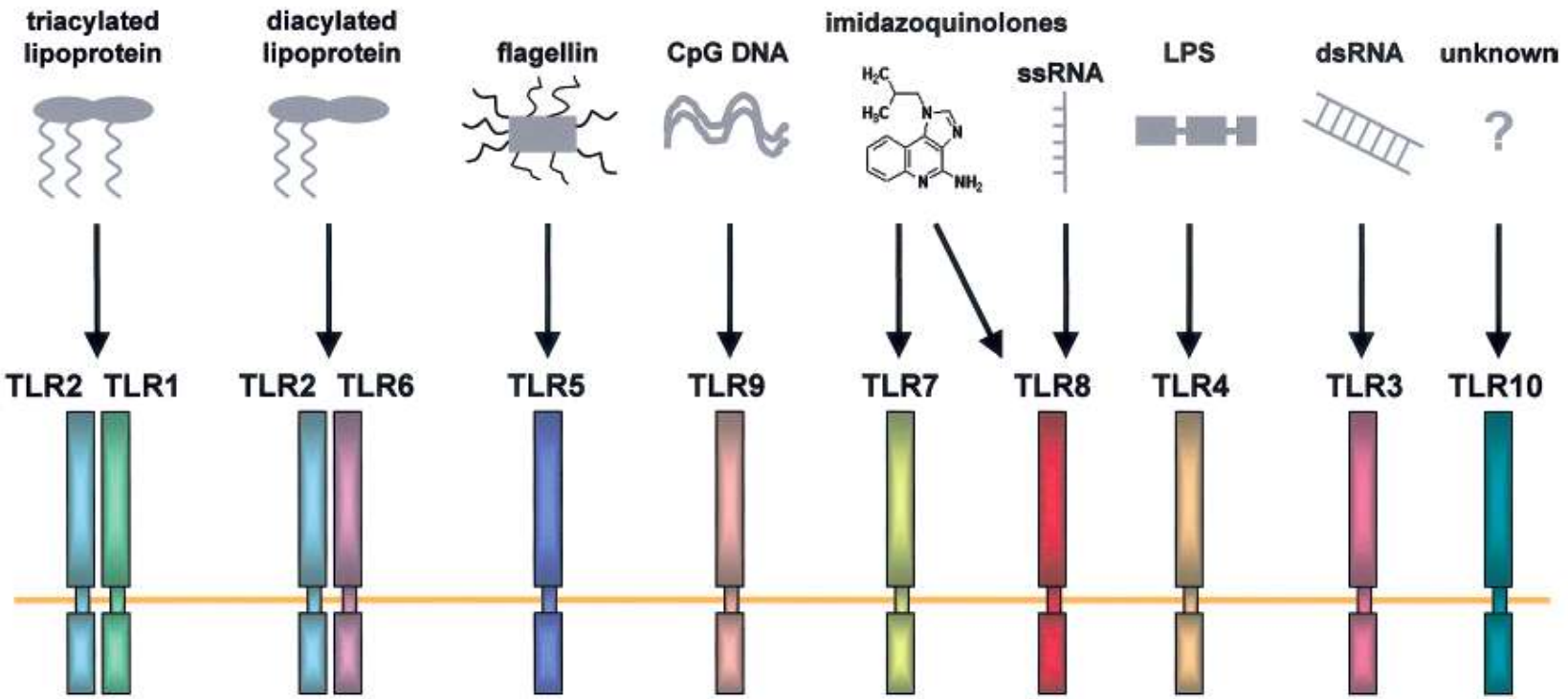


Figure 1
Human Toll-like receptors display specificity in their recognition of pathogen-associated molecular patterns and/or synthetic compounds.

Table I. Mammalian peptides and proteins relevant to skin with antimicrobial activity (AMP)[a]

	References
AMP identified in resident cells	
Cathelicidins	Frohm *et al* (1997), Marchini *et al* (2002)
β-Defensins	Harder *et al* (2001), Liu *et al* (2003)
Bactericidal/permeability-increasing protein (BPI)	Takahashi *et al* (2004)
Lactoferrin	Cumberbatch *et al* (2000)
Lysozyme	Marchini *et al* (2002)
Dermcidin	Schittek *et al* (2001), Murakami *et al* (2004)
RNase 7	Harder and Schroder (2002)
AMP identified in infiltrating cells	
Cathelicidins	Gallo *et al* (1994), Marchini *et al* (2002)
α-Defensins	Harwig *et al* (1994)
Lactoferrin	Caccavo *et al* (2002)
Granulysin	Stenger *et al* (1998)
Perforin	Stenger *et al* (1998)
Eosinophil cationic protein (ECP)/ RNase 3	Domachowske *et al* (1998a)
Eosinophil-derived neurotoxin (EDN)/RNase 2	Domachowske *et al* (1998b)
Regulated upon activation, normal T cells expressed and secreted (RANTES)	Tang *et al* (2002)

Table I. Continued

	References
Platelet factor 4 (PF-4)	Tang *et al* (2002)
Connective tissue activating peptide 3 (CTAP-3)	Tang *et al* (2002)
Platelet basic protein	Tang *et al* (2002)
Thymosin β-4 (Tβ-4)	Tang *et al* (2002)
Fibrinopeptide B (FP-B)	Tang *et al* (2002)
Fibrinopeptide A (FP-A)	Tang *et al* (2002)
AMP identified as proteinase inhibitors	
hCAP18/LL-37 prosequence (cathelin-like domain)	Zaiou *et al* (2003)
Secretory leukocyte proteinase inhibitor (SLPI)/Antileukoprotease	Wingens *et al* (1998)
Elafin/skin-derived antileukoprotease (SKALP)	Simpson *et al* (1999), Meyer-Hoffert *et al* (2003)
P-cystatin α	Takahashi *et al* (1994)
Cystatin C	Blankenvoorde *et al* (1998)
AMP identified as chemokines	
Psoriasin	Glaser *et al* (2001)
Monokine induced by IFN-γ (MIG/CXCL9)	Cole *et al* (2001a)
IFN-γ-inducible protein of 10 kDa (IP-10/CXCL10)	Cole *et al* (2001a)
IFN-γ-inducible T cell α chemoattractant (I-TAC/CXCL11)	Cole *et al* (2001a)

Antimicrobial peptides identified as neuropeptides	
α-Melanocyte stimulating hormone (α-MSH)	Cutuli *et al* (2000)
Substance P	Kowalska *et al* (2002)
Bradykinin	Kowalska *et al* (2002)
Neurotensin	Kowalska *et al* (2002)
Vasostatin-1 and chromofungin (chromogranin A)	Tasiemski *et al* (2002)
Secretolytin (chromogranin B)	Tasiemski *et al* (2002)
Enkelytin and peptide B (proenkephalin A)	Tasiemski *et al* (2002)
Ubiquitin	Kieffer *et al* (2003)
Neuropeptide Y	Lambert *et al* (2002)
Polypeptide YY/skin-polypeptide YY	Lambert *et al* (2002)
Adrenomedullin	Allaker *et al* (1999)
AMP identified based on other functions	
Hemoglobin-derived peptides	Parish *et al* (2001)
Calprotectin (MRP8/MRP14)/ calgranulin A/B	Sohnle *et al* (2000)
Neutrophil gelatinase-associated lipocalin (NGAL)	Goetz *et al* (2002)
Epidermal H1 histones	Kashima (1991)
Myeloperoxidase	Rosen and Michel (1997)

[a]References limited due to space restrictions.

Table II. Mouse models demonstrate that the chemokine family is important in host defense

Knockout	Clinical and immunological consequence Reference[a]	Microbe
Receptors		
CCR1		
	Reduced inflammation, increased mortality Domachowske, J Immunol, 2000	Paramyxovirus
	Increased susceptibility to infection Khan, J Immunol, 2001	*Toxoplasma gondii*
	Increased susceptibility to infection Gao, J Exp Med, 1997	*Aspergillus fumigatus*
	Smaller lesions containing fewer parasites Rodriguez-Sosa, Immunol Cell Biol, 2003	*Leishmania major*
	No effect on corneal PMN or opacities Hall, J Immunol, 2001	*Onchocerciasis*
CCR2		
	Defective macrophage recruitment and host defense Kurihara, J Exp Med, 1997	*Listeria monocytogenes*
	Decreased macrophage and CD8+ T cell recruitment Huffnagle, Immunopharmacology, 2000	*Cryptococcus neoformans*
	Prolonged pulmonary infection Up to 800-fold greater dissemination to spleen and brain Reduced macrophage recruitment Traynor, J Immunol, 2000	*C. neoformans*
	Failure to control infection Block in infection-induced relocalization of splenic DC Sato, J Exp Med, 2000	*Leishmania major*
	Significantly decreased survival Macrophages exhibit recruitment defects to lungs 100-fold higher bacterial load in lungs Peters, PNAS, 2001	*Mycobacterium tuberculosis*
CCR4		
	Decreased mortality in endotoxic shock Chvatchko, J Exp Med, 2000	LPS
CCR5		
	Impaired macrophage function ANCE Reduced efficiency in bacterial clear Zhou, J Immunol, 1998	*Listeria monocytogenes*
	No protection against infection or death Elvin Nature, 2004	*Yersinia*
	Decreased survival Defect in leukocyte migration to brain Huffnagle, J Immunol, 1999	*C. neoformans*
	Lower parasite burden in liver Sato, J Immunol, 1999	Leishmania donovani

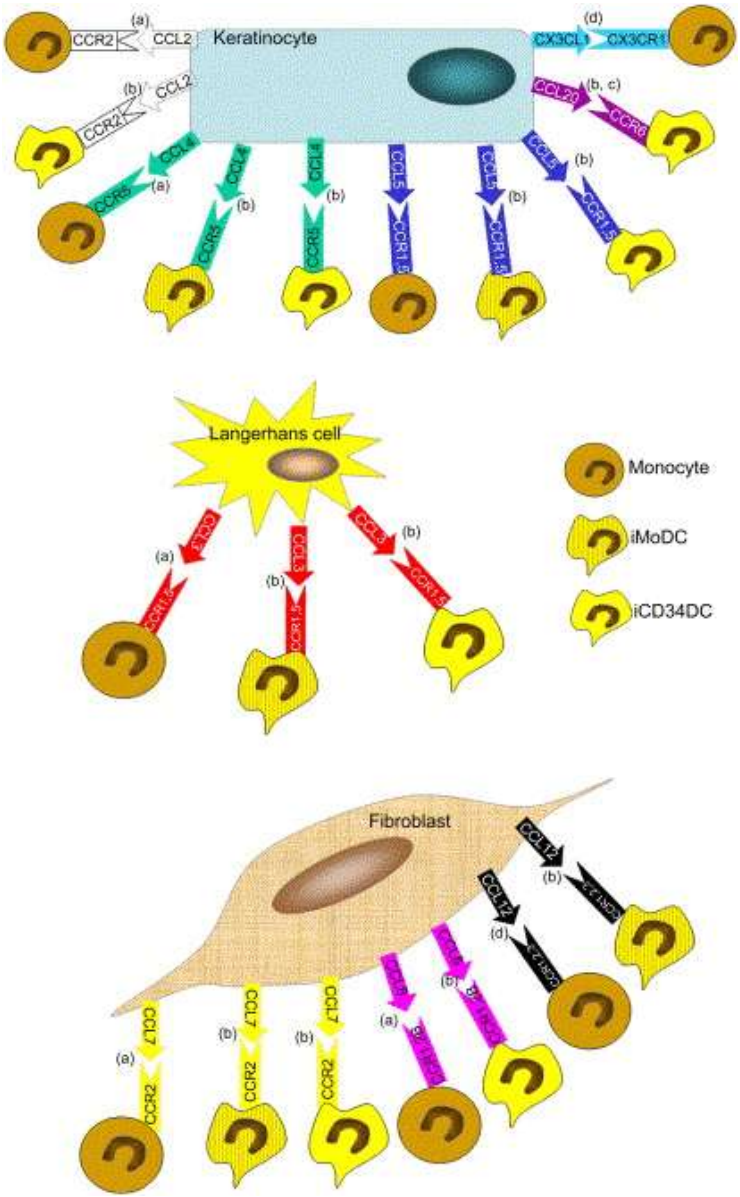
Table II. Continued

Knockout	Clinical and immunological consequence Reference[a]	Microbe
	Reduced macrophage infiltration Glass, Virology, 2001	Mouse hepatitis virus
	Antiviral T-cell response appears to be augmented Nansen, Immunobiology, 2002 Decreased susceptibility to Cryptosporidiosis Campbell, J Parasitol, 2002	Lymphocytic choriomeningitis virus Cryptosporidium parvum
	Decreased susceptibility to cerebral malaria Belnoue, Blood, 2003	Plasmodium berghei
IL8Rh/*CXCR2*		
	Dysfunctional neutrophil migration Godaly, J Immunol, 2000	*Escherichia coli*
	Subepithelial neutrophil entrapment and renal scarring Hang, J Infect Dis, 2000	*E. coli*
	Enhanced susceptibility to pyelonephritis Frendeus, J Exp Med, 2000 Frendeus, J Infect Dis, 2001	*E. coli*
	Impaired neutrophil recruitment Del Rio, J Immunol, 2001	*Toxoplasma gondii*
	Impaired neutrophil extravasation Increased bacterial burden Kielian, J Immunol, 2001	*S. aureus*
	Reduction in neutrophil recruitment Goncalves, Scand J Immunol, 2002	*Mycobacterium avium*
	Enhanced susceptibility to herpetic stromal keratitis Banerjee, J Immunol, 2004	HSV-1
	Decrease in Lyme arthritis severity ***Brown, J Immunol, 2003***	***B. burgdorferi***
	Decreased mucus production and airway hyperreactivity ***Miller, J Immunol, 2003***	***Respiratory syncytial virus***
CXCR5		
	Accelerated transfer of intraperitoneally administered prions into the spinal cord Prinz, Nature, 2003	Prions
DARC		
	Increased inflammatory infiltrates in lung and liver Dawson TC, Blood, 2000	LPS
Ligands		
CCL2		
	Reduced NKT cell recruitment Kawakami, J Immunol, 2001	*Cryptococcus neoformans*
	Enhanced susceptibility to gingivitis Chae, Infect Immun, 2002	*Streptococcus mutans*, *Streptococcus intermedius*, *Peptostreptococcus micros*, *Porphyromonas gingivalis*, *Prevotella intermedius*, *Fusobacterium nucleatum*

Table II. Continued

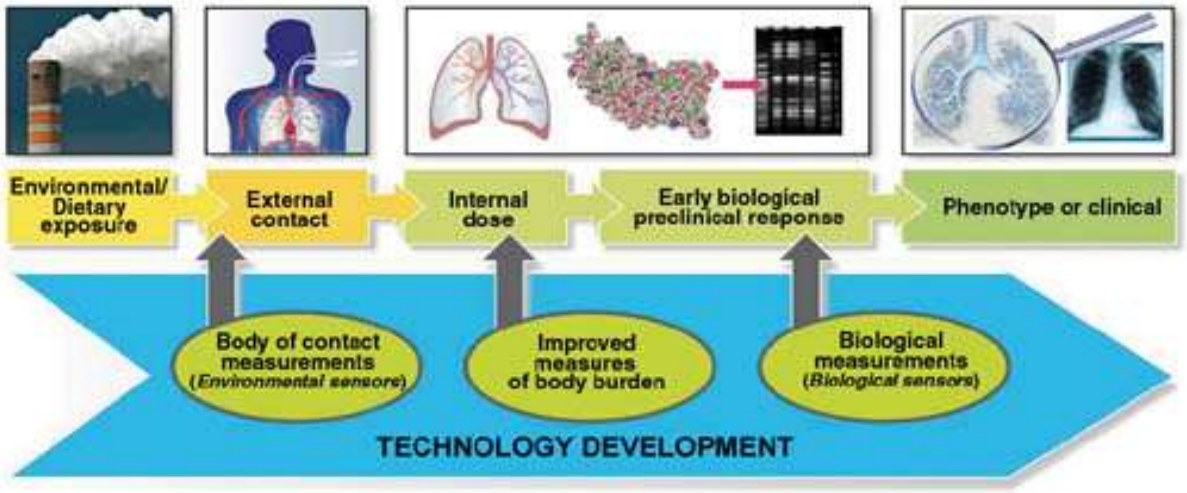
Knockout	Clinical and immunological consequence Reference[a]	Microbe
	Failure to expel infection deSchoolmester, J Immunol, 2003	*Trichuris muris*
CCL3		
	Reduced antiviral host defense Domachowske, J Immunol, 2000	Pneumonia virus
	Inhibited inflammatory and protective liver responses Salazar-Mather, J Exp Med, 1998	Murine cytomegalovirus
	Decreased resistance to infection Reduced NK cell accumulation Salazar-Mather, J Clin Invest, 2000	Murine cytomegalovirus
	Impaired survival Lindell, Infect Immun, 2001	*Klebsiella pneumonia*
	Decreased survival Olszewskin, J Immunol, 2000	*C. neoformans*
	Impaired prevention of eosinophilic pneumonia Olszewski, Infect Immun, 2001	*C. neoformans*
	Reduced protective innate immunity against sepsis Cecal ligation and puncture Takahashi, J Leuk Biol, 2002	*C. neoformans*
	Delayed viral clearance Trifilo, J Virol, 2003	Mouse hepatitis virus
	Lower parasite burden in liver **Sato, J Immunol, 1999**	***Leishmani donovani***
CCL11		
	Suppressed endotoxemia-associated peritoneal neutrophils Cheng, Exp Mol Pathol, 2002	LPS
CXCL15		
	Impaired pulmonary host defense Chen, J Immunol, 2001	*Klebsiella pneumonia*

Knockout mice (in bold) experienced *improved* survival advantage compared with wild-type mice.
[a]All references in this table can be found in the supplemental material available online for this article.


Keratinocyte
CCR2
CCL2
(a)
(b)
(d)
CX3CL1
CX3CR1
CCL20
(b, c)
CCR6
CCL4
CCR5
CCL5
CCR1,5
Langerhans cell
Monocyte
iMoDC
iCD34DC
Fibroblast
CCL7
CCR2

Balneoterapie – imunomodulační nástroj

- ✓ změna prostředí



Balneoterapie – imunomodulační nástroj

✓ stres

Mechanisms by Which Psychologic Stress Alters Cutaneous Permeability Barrier Homeostasis and Stratum Corneum Integrity

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Although many skin disorders, including psoriasis and atopic dermatitis, are adversely affected by psychologic stress (PS), the pathophysiologic link between PS and disease expression remains unclear. Recent studies demonstrated PS-induced alterations in permeability barrier homeostasis, mediated by increased endogenous glucocorticoids. Here, we assessed the mechanisms by which PS alters stratum corneum (SC) function. Insomniac psychologic stress (IPS) altered both barrier homeostasis and SC integrity. IPS decreased epidermal cell proliferation, impaired epidermal differentiation, and decreased the density and size of corneodesmosomes (CD), which was linked to degradation of CD proteins (e.g., desmoglein1). Barrier compromise was linked to decreased production and secretion of lamellar bodies (LB), which in turn could be attributed to a decrease in *de novo* synthesis of epidermal lipids. Topical physiologic lipids (equimolar cholesterol, ceramides, and free fatty acids) normalized both barrier homeostasis and SC integrity in IPS mice, further evidence that lipid deficiency accounted for these functional abnormalities. Thus, PS inhibition of epidermal lipid synthesis results in decreased LB formation and secretion, as well as decreased CD, compromising both permeability barrier homeostasis and SC integrity. These studies suggest that topical treatment with epidermal physiologic lipids could be beneficial in stress-induced, barrier-associated dermatoses, such as psoriasis and atopic dermatitis.

Key words: corneodesmosome/epidermal lipid synthesis/lamellar body/stratum corneum integrity/transepidermal water loss

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