World Rendez-Vous on Dermatology
by BIODERMA Foundation

UPDATES ON DERMATOLOGY

Edito

STÉPHANE FAUVERGHE
NAOS Global Medical Director

Dear All,

I am very pleased to present to you a new Updates dedicated to the latest advancements in Dermatology.

The World Rendez-Vous (WRDV) on Dermatology is an international event organised by the BIODERMA Foundation. The purpose of the WRDV is to strengthen connections within the medical community and provide a platform for sharing and exchanging ideas among dermatologists from around the world.

As part of our commitment to promoting the development of knowledge in Dermatology, we are pleased to offer you this new publication, which summarises a selection of the scientific sessions of the WRDV 2024:

- **The skin barrier, a protection of the self** – in this session, Enzo Berardesca (Rome, Italy) highlighted the key elements that make skin a more complete organ than just a barrier, and Kenji Kabashima (Tokyo, Japan) presented latest research on how keratinocytes and peripheral nerves communicate.
- **Skin microbiome: the infinitely small conductor of our organism,** where Richard Gallo (San Diego, USA) showcased the multiple roles of the skin microbiome within the whole skin ecosystem.
- **Pigmentary disorders and skin: new challenges and therapeutical advances** – this session covered the latest advances in the field, with Henry Lim (Detroit, USA) who presented the full spectrum of photoprotection options, from UVB to visible light; Sérgio Schalka (São Paulo, Brazil) highlighted key pathways and prevention methods for post inflammatory hyperpigmentation; Jorge Ocampo (San Pedro Garza García, Mexico) brought latest news in melasma; and Serge Dahan (Toulouse, France) shed light on how laser and intense pulsed light can benefit in pigmentation, photo-rejuvenation and more.

I wish you all an enjoyable, enriching, and insightful read.

SCIENTIFIC PROGRAMME

SPEAKERS' SHORT BIOGRAPHIES

ENZO BERARDESCA
ITALY

Enzo Berardesca is research professor at the Phillip Frost Dept of Dermatology, University of Miami. He has been Director of Clinical Dermatology at the San Gallicano Dermatological Institute, Rome, Italy from 2001 to 2017.

He is a past Chairman of the International Society for Bioengineering and the Skin and has organised numerous international conferences on skin bioengineering.

Dr Berardesca has published over 400 papers and 11 books, with a notable H-index of 54. He serves on the editorial boards of several leading dermatological journals and is Editor-in-Chief of Cosmetics.

SERGE DAHAN
FRANCE

Serge Dahan is a board-certified dermatologist specialising in lasers, energy-based devices (EBD), as well as aesthetic, medical, and surgical dermatology. He is the President of the Aesthetic Group of the French Society of Dermatology (SFD) and a former President of the Laser Group within the same society.

He has contributed significantly to the field through numerous scientific articles, textbook chapters, and coediting key textbooks, also serves on the editorial boards of dermatology journals and is actively involved clinical research. Currently, he is a member of the Scientific Committee of the BIODERMA Foundation.

RICHARD GALLO
USA

Dr Richard Gallo is a leading physician-scientist in dermatology, immunology, epithelial biology and microbiology.

Distinguished Professor at the University of California, San Diego, he discovered antimicrobial peptides in mammalian skin, revolutionising clinical medicine. His work on the skin microbiome has also contributed to our understanding of diseases such as atopic dermatitis and acne.

He has received numerous awards and is a member of prestigious scientific societies, with over 75,000 citations for his publications in leading journals.

KENJI KABASHIMA
JAPAN

Kenji Kabashima is a professor and chair of the Department of Dermatology at Kyoto University Graduate School of Medicine. He is also a princi-pal investigator at SRIS/A*STAR in Singapore and a visiting consultant at the National Skin Centre in Singapore.

His research focuses on the mechanisms behind inflammatory skin diseases, including atopic dermatitis, contact dermatitis, and psoriasis, using cutting-edge techniques like 3D skin visualization with two-photon microscopy.

His hobbies include marathons (his personal best is 2:54:38), trail running (Ultra Trail du Mont Blanc 170 km), golf, climbing, and traveling.

HENRY LIM
USA

Henry W. Lim is a dermatologist and former chair of the Department of Dermatology at Henry Ford Health in Detroit, Michigan, where he served from 1997 to 2017.

A past president of several major dermatological organisations, including the American Academy of Dermatology (AAD) and the International Union of Photobiology, Dr Lim was elected president of the International League of Dermatological Societies in 2023. He has published over 570 articles and edited 11 textbooks, with an h-index of 94 and numerous prestigious awards recognising his contributions to dermatology. He is a global leader in research on sunscreens and photosensitivity disorders.

JORGE OCAMPO
MEXICO

Jorge Ocampo Candiani is a dermatologist and member of the American Academy of Dermatology (AAD). He serves as Professor and Head of Dermatology at the Dr José E. González University Hospital, part of the Faculty of Medicine at the Autonomous University of Nuevo León.

A former President of the Iberian-Latin American College of Dermatology (CILAD), Dr Ocampo is also a co-founder of the Clinica Medipiel, a specialised Dermatology, Cosmetic & Laser Clinic. Additionally, he is a co-editor of Dermatología Cosmética, Médica y Quirúrgica (DCMQ). Dr Ocampo is currently organising the upcoming World Congress of Dermatology, which is set to be held in Guadalajara, Mexico, in 2027.

SÉRGIO SCHALKA
BRAZIL

Sérgio Schalka is a Brazilian dermatologist who obtained his medical degree from the University of São Paulo, where he also did his post-doc in dermatology. He then enriched his academic career with a master's degree in photoprotection, again at the University of São Paulo, before becoming a Visiting Researcher at the same university. His expertise in the field of photoprotection is particularly well recognised, and led him to become coordinator of the Brazilian Consensus on Photoprotection. He is also Head of the Photoprotection Laboratory at the Medcin Skin Research Center in São Paulo.

THE SKIN BARRIER, A PROTECTION OF THE SELF

THE SKIN, MORE THAN JUST A BARRIER

ENZO BERARDESCA
Miami, USA

INTRODUCTION

The skin is the largest human organ. It is in permanent contact with the environment and protects the body from sun rays, environmental pollution and infection. The skin barrier is composed of the *stratum corneum* (SC) and tight junctions (Figure 1). The mechanical protection, which is sometimes neglected, is one of the most important roles of the SC, as it regulates skin and body hydration, transepidermal water loss and maintains the temperature of the body.

Skin structure and composition

The physical barrier is made of corneocytes connected by corneodesmosomes and lipid-enriched intercellular domains. In addition to this physical barrier, a microbial, a chemical, an immunological barrier and a neuro-sensory barrier also exist.[1] The microbial barrier is made of commensal inhabitants of the skin. The chemical barrier is composed of molecules that contribute to hydration and the prevention of infections. The immunological barrier involves components of the innate immunity and the adaptive immune system. And the neuro-sensory system includes keratinocytes and ion channels expressed on the cutaneous level.[2]

The physical skin barrier

The nucleated epidermis contributes to the barrier through tight, gap and adherent junctions, as well as through desmosomes and cytoskeletal elements. During the epidermal differentiation, lipids are synthesised in the keratinocytes and extruded into the extracellular domains, where they form extracellular lipid-enriched layers. The cornified cell envelope, a tough protein/lipid polymer structure, resides below the cytoplasmic membrane on the exterior of the corneocytes. Ceramides A and B are covalently bound to cornified envelope proteins. They form the backbone for the subsequent addition of free ceramides, free fatty acids and cholesterol in the SC. Filaggrin is cross-linked to the cornified envelope, and aggregates keratin filaments into macrofibrils. Formation and maintenance of the skin barrier function is influenced by cytokines, 3',5'-cyclic adenosine monophosphate and calcium. Figure 2 shows the keratinocyte differentiation and maturation process resulting in a brick-and-mortar model.

Figure 1 - Skin barrier

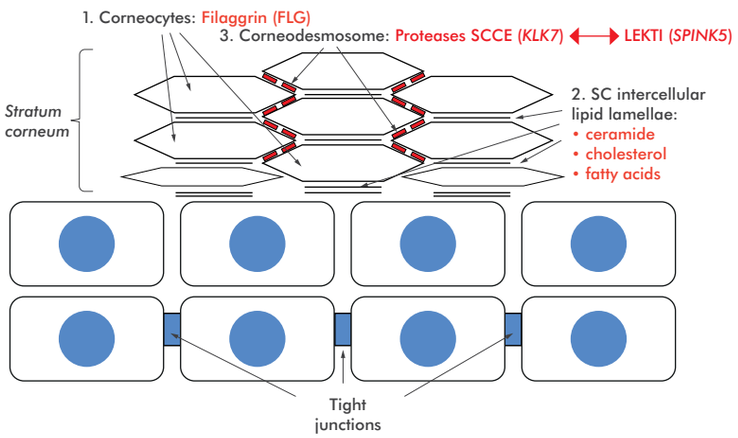
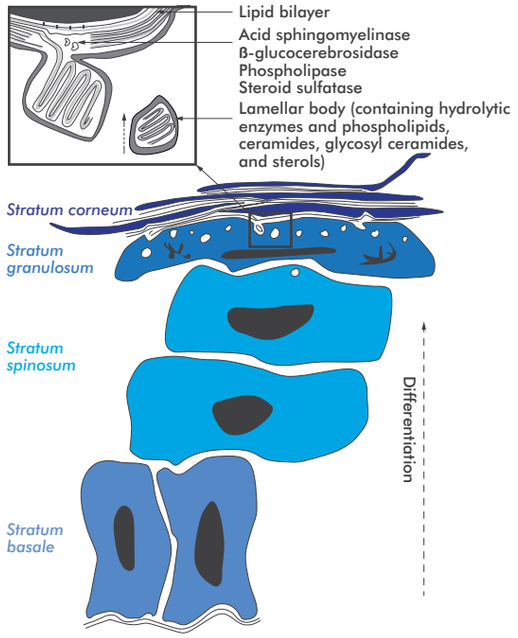


Figure 2 - Differentiation and maturation process of keratinocytes

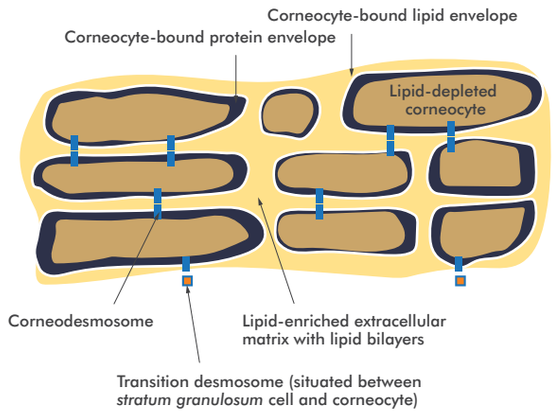


Corneocytes are wrapped in a protein envelope within a lipid-enriched extracellular matrix, with lipid bilayers (Figure 3). The cornified envelope replaces the plasma membrane of differentiating keratinocytes, and consists of keratins that are enclosed within an insoluble amalgam of proteins, such as envoplakin, involucrin, small proline rich proteins (SPR) and loricrin. There are two subtypes of corneocytes, one fragile, rough type found in the lower SC layers and one more rigid, flat type found in the superficial SC. The corneocyte envelope is formed by precursor proteins, which are crosslinked by transglutaminases and surrounded by a lipid envelope which interdigitates with intercellular lipid lamellae and is made of ceramides, cholesterol and free fatty acids.[3, 4]

Ceramides are thought to be derived from the lamellar granule-associated linoleate-containing acylglucosylceramide.[5, 6] It has been suggested that the corneocyte lipid envelope contributes to the chemical resistance of the SC, and serves as a template upon which the lamellae formed by the free SC lipids orient themselves. It may have a role in cohesion of the SC and may provide a semipermeable membrane around the corneocytes, allowing passage of water but preventing the loss of other larger hygroscopic substances. It also may serve as a reservoir of the antimicrobial free long-chain bases under certain microbial stresses. The acylglucosylceramide is also the precursor of the acylceramide found in the intercellular spaces of the SC. ω-hydroxyceramide is covalently attached to the cornified envelope.[7]

The lipid matrix in the human SC is organised in crystalline lipid lamellae: the short periodicity phase (SPP) with a repeat distance of around 6 nm and the long periodicity phase (LPP) with a repeat distance of around 13 nm. A lamellar phase consists of a series of repeating units referred to as the unit cell, with a length equal to the repeat distance. Within the plane perpendicular to the unit cell direction, these lipids can form either a very dense orthorhombic packing, a less dense hexagonal packing, or a disordered liquid packing. In the hexagonal packing, the lipids rotate along their longest axis. Finally, in the fluid phase, the distance between the lattice planes varies to some extent.[8] Other skin lipids include sebum, a waxy mixture

Figure 3 - Bricks and mortar model



predominantly composed of acylglycerols, wax esters, non-esterified fatty acids, squalene, cholesterol and cholesterol esters. The balance of these skin surface lipids in terms of their relative abundance, composition, molecular organisation and dynamics, as well as their intricate interactions, plays a crucial role in the maintenance of healthy skin. For that reason, **even minuscule alterations in skin surface lipid properties or overall lipid profile have been implicated in the etiology of many common skin diseases, including atopic dermatitis, psoriasis, xerosis, ichthyosis and acne.**[9, 10]

Desquamation is the result of a degradation of corneodesmosomes induced by different enzymes. It is controlled through pH and skin hydration regulation.[11] Enzymes that control desquamation include SC chymoytryptic enzyme (SCCE, KLK7), SC tryptic enzyme (SCTE, KLK5) and members of the cathepsin family, which is a group of 3 enzymes that act in the superficial layers at a low pH. Reductions of serine protease activity are a consistent theme in dry skin, and non-eczematous atopic dermatitis, otherwise known as atopic xerosis, leading to retention hyperkeratosis. Increased protease activity occurs in most, if not all, inflammatory dermatoses, ranging from the genetic disorders, psoriasis and eczematous atopic dermatitis, to sub-clinical barrier abnormalities induced by surfactants or environmental influences as a result of premature desquamation.[12]

Maintaining an acidic pH in the SC is important for establishing and maintaining a healthy skin barrier.[13] The SC exhibits a pH gradient, with a decrease in pH as it gets closer to the surface. To maintain the acidic mantle of the SC, sebum-derived free fatty acids and sweat-derived lactic acid are also important, as well as 3 endogenous pathways. These endogenous pathways include:

1. the non-energy-dependent Na+/H+ antiporter, NHE1,
2. the generation of free fatty acids from phospholipids by sPLA2, and
3. the generation of urocanic acid from histidine by histidase.

Deterioration of any of these pathways leads to an elevation in SC pH, which is linked to the alteration of permeability barrier homeostasis and SC integrity/cohesion (Figure 4).

Filaggrin is a critically important, multifunctional protein required for the normal biogenesis and physiology of the SC. It is synthesised from profilaggrin by a dephosphorilation step in the uppermost keratinocytes. Filaggrin deficiency correlates with the risk of eczema and atopic dermatitis. Within the squames, filaggrin undergoes further chemical modification and proteolytic processing to be eventually completely broken down to become a natural moisturising factor (NMF) – a pool of hygroscopic amino acids and derivatives thereof that act as a natural humectant within the residual cytoplasmic

Figure 4 - Mechanism for maintaining the pH within the stratum corneum

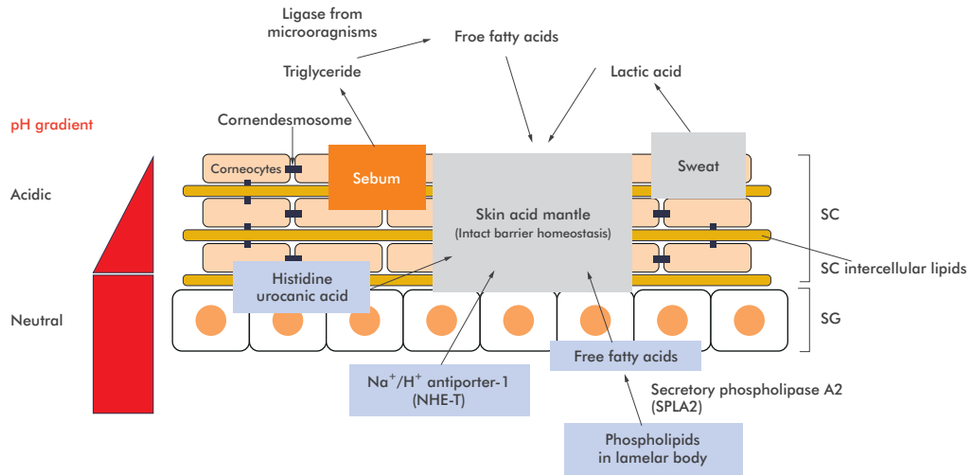
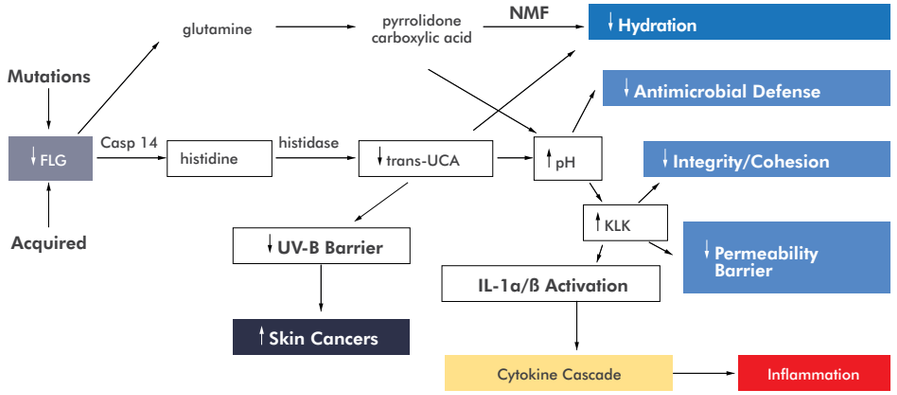


Figure 5 - Downstream Consequences of filaggrin deficiency leading to atopic dermatitis



space of the squames. **There is a strong correlation between the degree of genetically determined filaggrin deficiency and the likelihood of developing eczema.**[14-16] Figure 5 shows the downstream consequence of filaggrin deficiency leading to the cytokine cascade and ultimately to inflammation and atopic dermatitis.[16]

Factors triggering a disturbed skin barrier

Genetics and external factors play an important role in atopic dermatitis.[2] Filaggrin gene variants lead to a decreased NMF, which reduces SC hydration and increases pH. Increases in pH enhance protease (KLK5, KLK7 etc.) activity and inhibit lipid-generating enzymes. Together with defects in the genes encoding proteases and protease inhibitors (e.g. SPINK5), these changes increase the breakdown of corneodesmosomes, deregulate desquamation and impair lipid lamellae formation. Genetic changes in cornified envelope (e.g. FLG variants and SPRR3), lipid matrix (e.g. TMEM79) and tight junction (CLDN1) components may impair the structural integrity of the cornified envelope and lipid lamellae. Tight junction defects and increased pH impair the antimicrobial activity, increasing the probability of *Staphylococcus aureus* infections, which then worsen skin barrier breakdown. Environmental factors including soap, detergents and exogenous proteases further enhance protease activity, interacting with genetic defects, to break down the skin barrier. Once the skin barrier is impaired, the penetration of irritants and allergens into the skin increases, triggering skin inflammation and raising protease activity, leading ultimately to eczema and atopic dermatitis.[17]

The skin barrier is composed of the SC and tight junctions. In the SC, corneocytes, intercellular lipid lamellae, and corneodesmosomes are the major components of the skin barrier. Filaggrin is the main protein in the corneocyte. Ceramide is the most abundant lipid in the SC. Proteases, such as SCCE encoded by the KLK7 gene, degrade the corneodesmosomes. Serine protease inhibitors, such as LEKTI encoded by SPINK5, inhibit the protease activity. All of these are related to SC pH. A sustained increase in pH enhances the activity of degradatory proteases and decreases the activity of the lipid synthesis enzymes.[18] **The strong association between both genetic barrier defects and environmental factors aggress the skin barrier, suggesting that epidermal barrier dysfunction is a primary event in the development of this disease.**

Conclusion

In conclusion, the three main pillars of a well functioning skin barrier are filaggrin, a well-balanced equilibrium between a low level of proteases and a high level of protease inhibitors and the presence of skin lipids such as ceramides, cholesterol and free fatty acids. These 3 pillars allow for a well-regulated transepidermal water loss, a normal skin pH and an adequate skin hydration helping to maintain a well-functioning skin barrier. Disbalancing of one or all of these 3 pillars will lead to a disbalanced skin barrier inflammation and consequently to inflammatory skin diseases.

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COMMUNICATION BETWEEN PERIPHERAL NERVES AND KERATINOCYTES

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INTRODUCTION

There are five barriers in the skin, from the surface of the epidermis to the basement membrane (Figure 1): firstly, **the microbial barrier**, consisting of microbes and the *stratum corneum* (SC); secondly, **the physical barrier**, composed by the *stratum granulosum* with its intercellular junctions (tight junctions, adherens junctions and desmosomes); then, in the *stratum spinosum*, **the chemical barrier** actuated by the chemical response (AMP, NMF) and **the immunological barrier**, mediated by the innate and adaptive immune system; finally, **the neurosensory barrier**, operated by the peripheral nerve endings in the stratum basale.

Interaction between peripheral nerves and tight junctions during epidermal turnover.

Several types of peripheral nerves have been discovered in the mouse dorsal root ganglion by large-scale single-cell RNA sequencing.[1] In the epidermis, at least 11 types of peripheral nerves can be distinguished based on their mRNA expression profiles; the small-sized neuronal types NP1, NP2, NP3, PEP1, PEP2 and TH are thought to be involved in itch *via* multiple pathways (Figure 2). Among them, NP2 and particularly NP3 types show the strongest expression profile of itch receptors, such as *Il31ra, Trpv1* and *Hrh1*, and neuropeptides, such as *Nppb* and *Sst* (yellow cells in Figure 2), and may sense and transduce inflammatory pruritus. Of note, Th2 cells act on the sensory nerve *via* IL-31/IL-31RA, causing itch and exacerbating atopic dermatitis (AD). The IL-31 signaling pathway may represent a therapeutic candidate for pruritus in sensitive and very sensitive skin, as is the case in AD.[2]

To identify which types of peripheral nerves induce sensitive skin, it is important to understand their relationship with tight junctions in the epidermis. Each type of peripheral nerve has its own distribution profile: for example, NP1 and NP2 can pass across tight junction levels and penetrate the epidermis, while NP3, which expresses the IL-31 receptor, and PEP1 are mainly located in the dermis.

Dr Okada *et al.* published an important study concerning the relationships of peripheral nerves and tight junctions in human and mouse skin, using advanced immunohistology techniques and intravital imaging.[3] **In normal human epidermis, during epidermal turnover, peripheral nerves remain below the tight junctions level due to a pruning process, and the same is true in normal mouse skin. In contrast, in human AD and sensitive skin, the nerves can penetrate across the tight junctions into the epidermis**. Similarly, in Spade mice, an AD model with epidermal barrier impairment, tight junctions are almost abrogated, the pruning process is not performed properly during epidermal turnover and peripheral nerves even extend into the SC. This leads to aberrant activation of epidermal nerves, even by light touch, resulting in pathological itching. **Pruning of peripheral nerves, coordinated with tight junction replacement by keratinocytes, may contribute to skin sensory homeostasis and is important to prevent persistent peripheral nerve activation.**

Role of peripheral nerves and neuropeptides in restoring barrier function

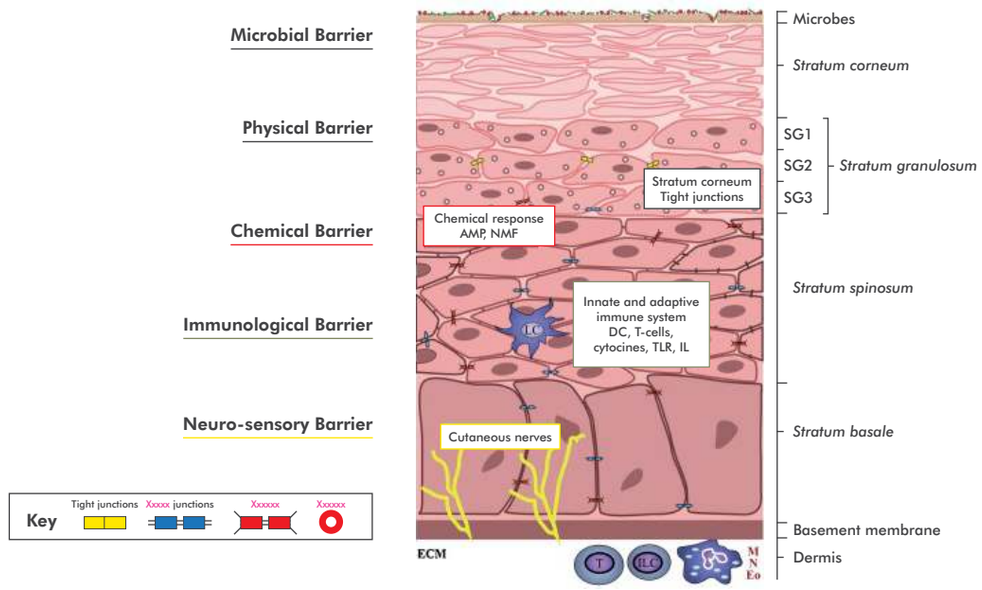
We recently published our results obtained in mice with resiniferatoxin (RTX), an ultra-potent capsaicin analog derived from a cactus-like plant that acts as an agonist of the TRPV1 receptor, inactivating TRPV1 signaling in peripheral nerves.[4] RTX is also considered a promising therapeutic target for analgesia, due to its ability to induce cytotoxicity in sensory neuronal cell bodies expressing the TRPV1 ion channel. RTX treatment in mice resulted in impaired nocifensive behavior, measured as the number of times the eye was wiped in a capsaicin-induced eye wipe test, suggesting that after RTX treatment peripheral nerves are inactivated and feel less pain and itch. RTX treatment did not affect keratinocyte proliferation or differentiation[4] Figure 2 provides a schematic view of the experimental system and the main results.

Firstly, the effect of peripheral nerves on the time course of epidermal barrier recovery was investigated. After skin barrier disruption by tape stripping, RTX-treated mice exhibited prolonged elevation of both trans epidermal water loss (TEWL) and skin surface pH, compared to rapid recovery in untreated animals. Similarly, prolonged TEWL elevation was observed in Nav 1.8-Cre R26-CAG-LoxP-EGFP-TeNT mice (in which exocytosis from C- and A-delta fiber sensory nerves was blocked by tetanus toxin expression) compared to controls. These results suggest that recovery of the epidermal barrier is dependent on TRPV1+ sensory nerves[4].

mRNA expression experiments showed that the expression of *Flg*, a keratinocyte differentiation marker, and *Elov14*, which is involved in ceramide synthesis, decreased in the RTX-treated mice but not in the control mice after tape stripping, while the expression of *Ocln*, a component of tight junctions, was not significantly different. These findings suggest a possible link between *Flg* and *Elov14* mRNA expression and TRPV1-positive nerves.

Cytokine signaling (IL-4, IL-5, IL-6, IL-13 and STAT3) was activated in RTX treated mice after tape stripping, compared to vehicle-treated animals. Then the protein and mRNA expression of the inflammatory cytokines IL-5, IL-6 and IL-13, which are suppressors of epidermal barrier protein expression, in the skin of RTX-treated mice and controls was investigated. After tape stripping, the expression of the three proteins showed a sustained elevation in treated compared to control mice.

Figure 1 - The five types of skin barrier



Source: Luger, Thomas *et al.* Journal of Dermatological Science, Volume 102, Issue 3, 142 - 157.

Figure 2 - Expression profile (fraction of positive cells by thresholding method) of itch receptors and neuropeptides in small size neurons[1]

	Population: *N*: 1 cell represents:	NP1 125 0.008	NP2 32 0.03	NP3 12 0.08	PEP1 64 0.016	PEP2 17 0.06	TH 233 0.004
Symbol	Ratio to Actb						
Itch receptors							
Mrgprd	0.06	0.84	0.22	0	0.02	0	0.01
Trpa1	0.04	0.51	0.22	0.17	0.06	0	0.18
Lpar3	0.07	0.66	0.03	0	0	0	0.01
Lpar5	0.05	0.24	0.03	0.08	0	0	0.01
Mrgpra3	0.11	0.01	0.63	0.08	0	0	0
Mrgprx1	0.05	0.07	0.53	0.33	0	0	0
Cysitr2	0.12	0.03	0	0.67	0	0	0
Il31ra	0.06	0	0.03	0.58	0.02	0	0
Osmr	0.09	0.01	0.38	0.75	0.03	0	0.01
Trpv1	0.09	0.03	0.28	0.58	0.31	0	0
Hrh1	0.02	0	0.09	0.08	0	0	0
Htr2a	0.02	0.07	0.03	0.25	0.02	0.24	0
Htr1f	0.02	0	0.09	0.83	0	0	0
Htr3a	0.31	0	0.12	0	0.05	0.82	0
Neuropeptides							
Nmb	0.21	0.94	0.75	0.67	0.39	1.00	0.16
Calca	1.97	0.20	0.88	0.08	0.78	1.00	0.01
Nppb	0.30	0	0.03	0.83	0.03	0	0
Sst	0.39	0	0.03	0.83	0.02	0	0
Agrp	0.03	0.01	0.13	0.25	0.11	0	0
Nts	0.35	0.01	0.03	0.75	0.02	0	0
Tac1	11.94	0.03	0.09	0.17	0.83	0	0.04
Adcyap1	0.19	0.01	0.09	0	0.63	0	0.01

The population size and the fraction of the population that would correspond to one cell are shown at top.

On the other hand, mRNA expression was statistically significantly higher in RTX-treated mice only for IL-6, but not for IL-5 or IL-13, showing that IL-6 expression is differentially enhanced by peripheral nerve inactivation[4]. Results suggest that inflammation may play a role in delayed barrier recovery in RTX-treated mice.

Screening of the expression of a battery of several neuropeptides in the dorsal root ganglia of RTX-treated mice and controls after tape stripping showed that the mRNA expression of some neuropeptides was significantly downregulated in RTX-treated mice compared to controls, namely *Adcyap1* (PACAP), *Gal* (galanin), *Nms* (neuromedin), *Sst* (somatostatin) and *Tac1* (substance P).[4] In another experiment, mouse primary keratinocytes showed relatively high expression of some receptors of PACAP, somatostatin and galanin during differentiation promoted by high calcium concentration.[4] **These results suggest that after skin barrier disruption, the peripheral nerves are activated and produce neuropeptides or other mediators to promote barrier recovery and suppress inflammation, especially during terminal differentiation of keratinocytes.**

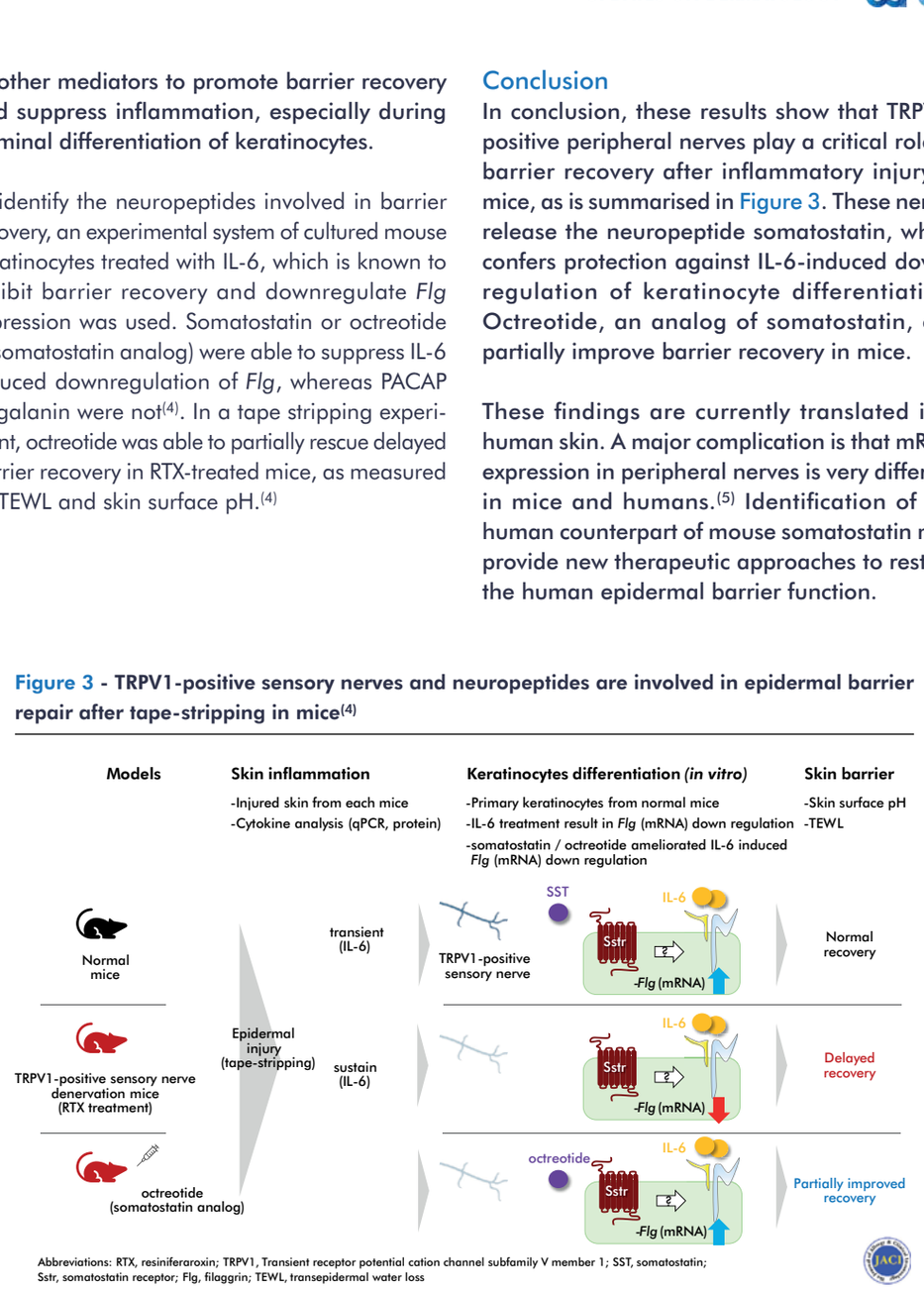
To identify the neuropeptides involved in barrier recovery, an experimental system of cultured mouse keratinocytes treated with IL-6, which is known to inhibit barrier recovery and downregulate *Flg* expression was used. Somatostatin or octreotide (a somatostatin analog) were able to suppress IL-6 induced downregulation of *Flg*, whereas PACAP or galanin were not[4]. In a tape stripping experiment, octreotide was able to partially rescue delayed barrier recovery in RTX-treated mice, as measured by TEWL and skin surface pH.[4]

Conclusion

In conclusion, these results show that TRPV1-positive peripheral nerves play a critical role in barrier recovery after inflammatory injury in mice, as is summarised in Figure 3. These nerves release the neuropeptide somatostatin, which confers protection against IL-6-induced down-regulation of keratinocyte differentiation. Octreotide, an analog of somatostatin, can partially improve barrier recovery in mice.

These findings are currently translated into human skin. A major complication is that mRNA expression in peripheral nerves is very different in mice and humans.[5] Identification of the human counterpart of mouse somatostatin may provide new therapeutic approaches to restore the human epidermal barrier function.

Figure 3 - TRPV1-positive sensory nerves and neuropeptides are involved in epidermal barrier repair after tape-stripping in mice[4]



Abbreviations: RTX, resiniferaroxin; TRPV1, Transient receptor potential cation channel subfamily V member 1; SST, somatostatin; Sstr, somatostatin receptor; Flg, filaggrin; TEWL, transepidermal water loss

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SKIN MICROBIOME: THE INFINITELY SMALL CONDUCTOR OF OUR ORGANISM

THE SKIN MICROBIOME FROM THE POINT OF VIEW OF THE SKIN AS AN ECOSYSTEM

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INTRODUCTION

Over the last decades, the gut and skin microbiome have gained much interest, and a lot of false promises have been made about them. This resume provides some of the fundamentals about the interaction between the human body, especially the skin barrier, and skin microbiome.

Biomes and ecosystems

Biomes refer to living organisms, and microbiome refers to microbes in a given space. These microbes could be bacteria, viruses, fungi and parasites. **Each microbiome acts like an ecosystem, which can be defined as the interaction of organisms, and which consists of all life forms within that physical space. Thus, an ecosystem refers not only to its inhabitants, but also to the local environment to which it is exposed. As a result, skin health and dermatology should also include the ecosystem rather than just the skin barrier or its commensal microbes.**

The human body has many different skin ecosystems, including oily and sebaceous, as well as moist or dry ecosystems, which are all very different microbiome compositions or ecosystems.

Over recent years, technology in microbiome research has rapidly advanced.[1] Some of the first important hypotheses about the skin microbiome were made in the 1960s, when, for the first time, Marples described the skin as a diverse ecosystem with many different microbes living on it.[2] In the late 1970s and early 1980s, work showed that in patients with atopic dermatitis, *Staphylococcus* strains were more frequently observed than in healthy skin.[3, 4] These basic observations allowed technology to accelerate, with genome sequencing using 16 rRNA analysis leading to the human skin genome analysis in 1985.[5, 6] The Human Microbiome Project, launched in the early 2000s, allowed to gain more and more insights into human microbiomes using amplicon sequencing and shotgun metagenomics.[7-11]

The skin microbiome

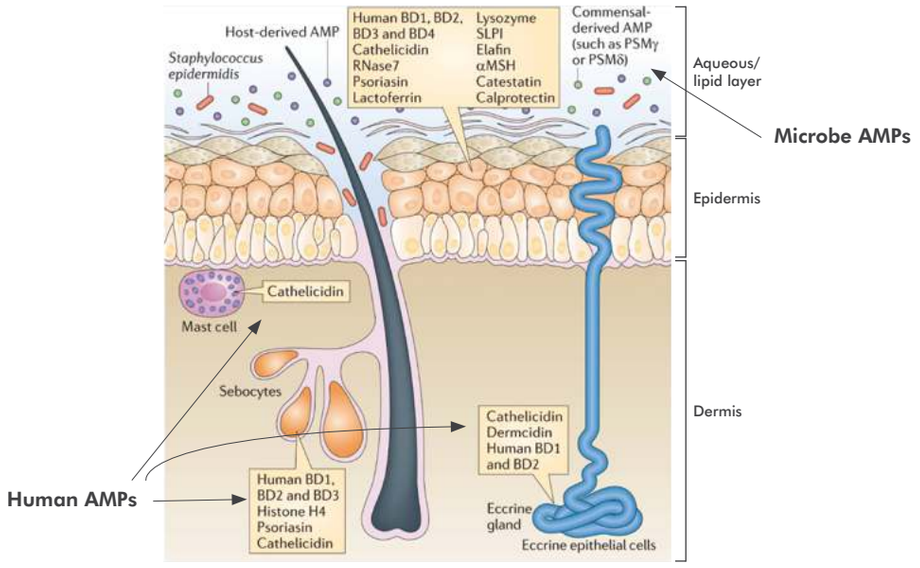
The surface of the human skin as an organ is about 30m², corresponding to the size of the human intestine.[12] However, it greatly differs from the intestine, which is an equilibrium of microbes, feces and other elements.

On the skin surface layers, microbes can be rapidly eliminated using an appropriate antiseptic. However, the skin contains follicular structures protected by lipids, offering a shelter to most of their inhabitants. In these shelters, bacteria are protected from external aggression, detergents and antibacterials, and proliferate, creating an interaction between them and the host, being important for skin and overall body health.[9]

The skin microbiome consists of commensal and opportunistic (pathogenic) inhabitants. The balance between these two categories of inhabitants results in a healthy skin barrier. The gut microbiome produces mucus to protect itself from proliferation of opportunistic inhabitants through the release of natural antibacterials, preventing them from penetrating the tissue. Conversely, in the skin, harmful bacteria can penetrate the epidermis and reach the dermis. To fight against this invasion, each of the different skin cell types, including adipocytes, can produce a variety of antimicrobial peptides (AMPs) including cathelicidin, dercidin, Human BD1 and BD2, as well as psoriasin, lysocyme and many others (Figure 1). The skin cells do not only indiscriminately release AMPs: they also release them when required.[13, 14]

In addition to AMPs released by the host, commensal bacteria also release AMPs, thus controlling the over-colonisation of competitive pathogens.[10] In 1974, Leyden showed that in patients with atopic dermatitis, the total bacteria load, particularly that of *Staphylococcus (S.) aureus*, is significantly larger than that of healthy skin areas.[15] DNA-based measures performed in 2012 confirmed that **the *S. aureus* load in atopic dermatitis lesions is considerably larger than that of other *Staphylococcus* strains, confirming a disbalanced microbiota composition.[16] DNA sequencing of skin samples identified specific genes of *S. aureus* that damage the skin by producing the toxin Phenol-soluble modulin (PSM).[17] PSMs trigger immune responses, mast cells and degranulation, while recruitment of neutrophils increases inflammation, leading to atopic dermatitis.[18] Moreover, *S. aureus* produces enzymes that cleave proteins, causes them to break down the skin barrier, cleaves certain molecules which act as direct stimulators in itch, and also amplifies the allergic inflammation at the IL4-IL13 response level (Figure 2).[19, 20]**

Figure 1 - Control of the skin microbiome through antimicrobial peptides (AMPs)



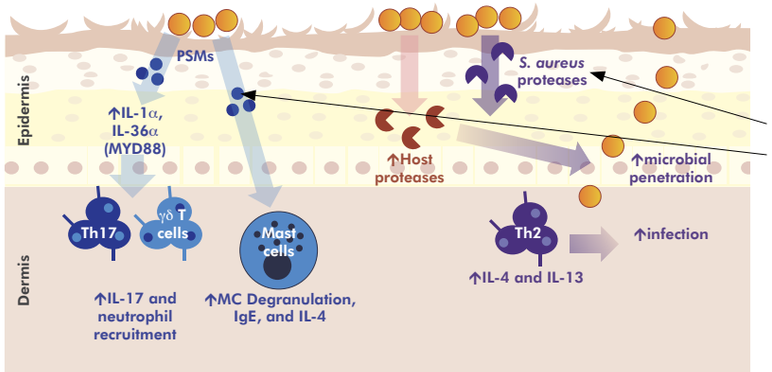
The role of beneficial bacteria

The role of beneficial bacteria in atopic dermatitis was shown in a phase 1, double-blinded, randomised 1-week study that investigated the safety and mechanisms of action of *S. hominis A9* (*Sh*A9), a bacterium isolated from healthy human skin, as a topical therapy for atopic dermatitis on the forearm skin of 54 adults with *S. aureus*-positive atopic dermatitis. *Sh*A9 killed *S. aureus* on the skin of mice, and inhibited expression of a toxin from *S. aureus* (*psma*) that promotes inflammation.[21] Severity of atopic dermatitis was not significantly different when evaluated in all participants treated with *Sh*A9, but a significant decrease in *S. aureus* (-99% *vs*. none with the placebo) and skin redness improved by 75% compared to 20% with the placebo. *Sh*A9 DNA *S. aureus* strains on participants were not directly killed by *Sh*A9, but expression of mRNA for *psma* was inhibited in all strains. Improvement in local atopic dermatitis severity was suggested by post-hoc analysis of participants with *S. aureus* directly killed by *Sh*A9. **ShA9 therapy was well tolerated, with no adverse events reported. These observations demonstrate the safety and potential benefits of bacteriotherapy for atopic dermatitis, as is also demonstrated in other work.**[22]

Conclusion

The skin microbiome is an ecosystem that controls the growth of non-commensal pathogens and of beneficial commensal skin inhabitants. It is important to the health of the skin and to that of the entire body. Rebalancing the natural composition of the skin microbiome and the ecosystem is essential to improve inflammatory skin diseases.

Figure 2 - *Staphylococcus aureus* genes and functions that harm the skin



Specific genes identified in *S. aureus* that damage the skin

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PIGMENTARY DISORDERS AND SKIN: NEW CHALLENGES AND THERAPEUTICAL ADVANCES

PHOTOPROTECTION: FROM UVB TO VISIBLE LIGHT

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How many types of sunscreen products are available in the world? A recent paper addresses this question, particularly regarding the similarities and differences between the USA and the European Union (EU).[1]

In the USA, there are 17 FDA-approved UV filters, 16 of which are described in FDA Monographs and are on the market. One, ecamsule, is no longer marketed according to the manufacturer's decision, because it was approved through the New Drug Application process, which requires strict adherence to the specific approved formulation.

29 UV filters have been approved in the EU, of which 18 are only approved in the EU, while the other 11 are marketed in both the USA and the EU. Only 6 UV filters are marketed exclusively in the USA. This represents a significant disadvantage in the number of filters that manufacturers can include in their sunscreens for marketing in the USA, compared to the EU.

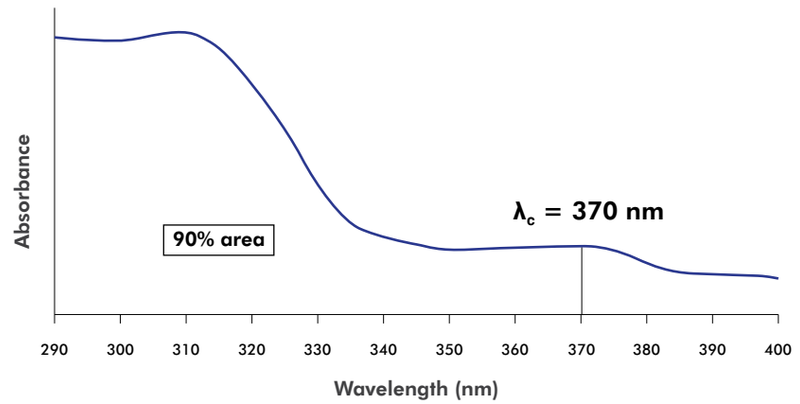
In terms of the spectral absorbance of the various filters, **UVB and broad spectrum (UVA+UVB) filters are the most common in both the USA and the EU.** Regarding UVA-only filters, there are two brand new filters in the EU: Mexoryl® 400, which covers long-wave UVA1, and TriAsorB®, which covers both UVA1 and visible light. Avobenzone has long been marketed in both the USA and EU, and covers both UVA2 and UVA1. It is the only UVA filter marketed both in the USA and EU. Finally, Meradimate® is a UVA filter available exclusively in the USA, and covers UVA2.

The Sun Protection Factor (SPF) is a system used around the world to measure a filter's protection against UV (primarily UVB but also UVA2, which is responsible for the sunburn reaction). SPF reflects the minimal erythema of sunscreen-protected skin compared to non-sunscreen-protected skin.

For UVA, the measure of photoprotection varies in the USA and the EU. In the USA, UVA-PF measurement is based on the critical wavelength (λc) being at 370 nm or above. An explanation of critical wavelength for a hypothetical sunscreen is shown in Figure 1. In this example, 90% of the UV absorbance area under the curve is at 370 nm: this is the critical wavelength of this product, thus considered broad spectrum by the USA standards. However, this system allows to have a very long critical wavelength when including a lot of UVA filters. To ensure a balanced protection against both UVA and UVB, this system still needs to be combined with another system, for example a UVA1/UVA+UVB absorbance ratio equal or greater than 0.7, which has not yet been approved by the FDA.

In the EU, a widely used system to indicate UVA protection is to calculate one third of the SPF. For example, an SPF 30 sunscreen has a UVA protection factor of 10 or above, and an SPF 45 sunscreen has a UVA protection factor of 15 or above. Another system used in the EU is the persistent pigment darkening (PPD) method, which compares the effect of radiation on sunscreen-protected and unprotected skin. A difference between these methods is the inclusion or exclusion of visible light, as discussed in the next section.

Figure 1 - The critical wavelength of a hypothetical sunscreen



To summarise, there is currently no standard measure of photoprotection accepted by regulatory agencies worldwide. A consensus conference will be held in September 2025 to produce a consensus statement on this topic and thereby fill the gap.

Visible Light

The spectrum of sunlight reaching the Earth's surface ranges from a wavelength of 290 nm to more than 2400 nm. UV has the lowest wavelength, from 290 to 400 nm, and represents only 2% of the sunlight reaching the Earth's surface. However, UV has the greatest biological significance and has been studied the most. Visible light (400 to 700 nm) represents 47% of the sunlight reaching the Earth's surface. The rest (700 nm to 1 mm) is infrared, the part that heats skin.

In a study published a few years ago, the effect of UVA1 *versus* visible light on different skin types was studied.[2] When skin types IV to VI were exposed to pure visible light, a significant pigmentary alteration appeared immediately and lasted for one week. When the same skin type was exposed to UVA1, there was an immediate pigment darkening that disappeared almost completely in one week. In contrast, when visible light was applied to type II skin, there was no alteration in pigmentation at all. Subsequently, it was shown that the active spectrum is mainly in the blue light range via opsin-3, a key sensor in melanocytes.[3, 4] Blue light activates opsin-3, leading to the formation of the tyrosinase/tyrosinase-related protein complex. Opsin-3 is abundant in melanocytes of dark-skinned individuals and induces sustained tyrosinase activity.

Obviously, in the real world, individuals are exposed not only to visible light but to the entire spectrum of sunlight. Therefore, the effects of visible light + UVA1 *versus* pure visible light on pigment darkening were compared[5]. **Visible light + UVA1 was shown to have a synergistic effect on pigment darkening that was more intense than visible light alone, both immediately (on Day 0) and over time, up to 14 days after exposure. This underscores the importance of developing sunscreens that can protect not only against UVA and UVB, as shown above, but also against visible light.**

The most widely used sunscreens in the USA and in many other parts of the world are tinted sunscreens, which contain pigments such as iron oxides and sometimes titanium dioxide. **Tinted sunscreens protect against visible light and long-wave UVA1, but they have important limitations. For example, the darker skin type shows significant skin whitening after application of 1 or 2 mg/cm², which is obviously not acceptable for many patients (2 mg/cm² is the concentration recommended by the main regulatory agencies in the world).**[5]

Recently, new filters have been developed that cover both UVA and visible light. Some examples are Mexoryl® 400 and TriAsorB®, which are

available in the EU but not in the USA. Another example is BDBP. This filter was developed and even approved by EU regulators but has not been commercialised. Another compound is extracted from *Polypodium leucotomos* and is used as an oral formulation. It has been shown to down-regulate visible light-induced pigmentation.

Finally, topical antioxidants can also be used for photoprotection. The rationale is that more than half of all free radicals from sunlight are generated by visible light.[6] Two years ago, an interesting study was published. This study observed **the effect of the topical application of an antioxidant blend on skin of different phototypes.** [7, 8] **After irradiation with visible light+UVA1, both skin types I-III and IV-VI showed a decrease in pigment darkening or erythema immediately on Day 0 compared to the untreated skin, and the difference was evident by Day 7.** The list of antioxidants that can be used in sunscreens is long and includes niacinamide (vitamin B3), licochalcone A, carotenoids (beta-carotene), vitamin E, vitamin C, glycyrrhetinic acid and diethylhexyl syringylidene malonate (DESM).[8]

Personalised Photoprotection

Personalised photoprotection has been the subject of two of my recent publications.[9, 10] This concept stems from the simple observation that we all have different skin types and different activities, and therefore the dermatologist's recommendation to the public and patients must be personalised.

Individual differences that affect the need for photoprotection include skin phototype, age, time spent outdoors or indoors for work or leisure, altitude and latitude, and pollution levels, which also affect skin aging. Another important factor is the microbiome, which produces compounds that help protect the skin from UVR, while some sunscreens have the potential to reduce the diversity of the skin microbiome.[11] **Sunscreens that both protect against UVR and preserve the skin microbiome may provide additional skin health benefits.**

Sunscreens should be calibrated for different phototypes as shown in Figure 2. For example, a patient with dark skin may need high protection against visible light but not against UVB.[12] Interactions between biological, environmental and lifestyle factors are now being studied and recognised.[9]

Conclusion

In conclusion, the dermatologist's recommendations for photoprotection should always include general advice such as staying in the shade, wearing appropriate clothing and hats, and using a parasol. In addition, when it comes to sunscreens and sometimes oral photoprotection, recommendations need to be personalised and tailored to each individual.

Figure 2 - Spectral absorbance profiles of sunscreens for different skin phototypes[12]

Fitzpatrick phototype	Description	Individual Typology Angle (ITA)	Skin color (ITA classification)	UVB protection (SPF)	UVA protection (UVA-PF)	High energy visible light protection (VL-PF)
I	Always burns, never tans	ITA° >55°	Very light	SPF50+	UVA-PF +++ (>1/3 labelled SPF)	
II	Bums easily, sometimes tans	41° <ITA° <55°	Light			
II	Sometimes burns, always tans	28° <ITA° <41°	Intermediate			
IV	Rarely burns, tans easily	10° <ITA° <28°	Tan			
V	Rarely burns tans easily; moderately pigmented	-30° <ITA° <10°	Brown			
VI	Rarely burns, tans promptly and intensely; highly pigmented	ITA° <-30°	Dark	SPF30+	UVA-PF +++ (> 2/3 labelled SPF)	VL-PF+++

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POST INFLAMMATORY HYPERPIGMENTATION

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INTRODUCTION

Post-inflammatory hyperpigmentation (PIH) is a common pigmentary disorder caused by cutaneous endogenous inflammation, external injury, or cutaneous procedures.[1, 2] For example, acne, insect bites or dermatological procedures may trigger PIH.

Epidemiology

Concrete data about the prevalence of PIH are missing. However, PIH is more frequently observed among patients with Fitzpatrick skin phototypes III to VI – or skin of colour – than in those with skin type I to III.(3-7) It is currently estimated that pigmentation disorders are the 11th most common condition observed by dermatologists.[8, 9] Several studies have reported that PIH, including acne-induced PIH (AI-PIH), is most common in African American (20% of diagnosed PIH cases) and Hispanic populations (6.0%-7.5%).[10, 11]

In a study conducted by Perkins *et al.* including 2895 subjects (384 African American, 520 Asian, 1295 Caucasian, 258 Hispanic and 438 Continental Indian), the prevalence of AI-PIH was reported to be 65%, 48% and 25% for African American, Hispanic and Caucasian patients, respectively.[12] A study conducted in China reported that PIH after laser resurfacing reported a prevalence of 11.1% to 17.1% of all examined subjects.[13] After ablative fractional CO_2 laser treatment, the incidence of PIH was 23% in subjects with a phototype I-III, and 92% in subjects with a phototype of III and above. [14]

Globally, only 15% of the population worldwide can be qualified as individuals of non-skin of color (i.e. Caucasians), while the remaining 85% is comprised of individuals who have darker skin hues (such as Asians, Africans, Native Americans, and Pacific Islanders.[15])

Hyperpigmentation types

Hyperpigmentation may be subdivided into epidermal, dermal, or mixed epidermal-dermal disorders, based on the location of pigment deposition, along with disorders of hyperpigmentation of the mucosa and nails. **Epidermal PIH is characterised by light to dark brown patches**, which usually appear within months or years, and which improve with treatment. Pigmentation is increased in the basal epidermal layer. **Dermal PIH is characterised by blue or blue-grey patches**. Its course may be prolonged and may be permanent. **In dermal PIH pigmentation, a marked melanin pigment incontinence is observed in the dermis, with a non-increased basal epidermal pigmentation level**[1,16] Using UV light and Wood's lamp helps to analyse the level of hyperpigmentation through visualisation of epidermal melanin, and distinguishes epidermal from dermal PIH.[1]

PIH Pathways

Major pathways involved in PIH include the release of inflammatory cytokines from keratinocytes, and growth factors from dermal fibroblasts. Following the production of melanin, its deposition in the dermis can occur in two ways:[1] Melanin can directly be deposited into the dermis through the gaps in basal lamina;[2] macrophages engulf melanin in the epidermis; these melanophages migrate from the epidermis to the dermis, which contribute to dermal pigmentation.[17]

Dark skin demonstrates unique characteristics regarding epidermal morphogenesis, secretory activity in the dermis and the architecture of dermal-epidermal junctions that are distinctive from light skin. A predisposition to low-grade chronic inflammation and weaker macrovascular function has been also detected in dark-skinned individuals. Abnormal melanogenesis is furthermore exasperated by UVR; both the UVR-induced inflammation and cell senescence have been demonstrated to drive age-related hyperpigmentation.[18] Figure 1 shows the different factors that may lead to PIH in dark skin.

PIH triggering factors

Different factors trigger PIH. While sun exposure is not necessarily a predisposing factor to PIH, it may worsen it.[19] While UVB is less relevant during the pigmentation process, UVA 1 and high energy visible light (HEVL) heavily impact pigmentation.

UVR, especially UVA, increases the thickness of the *stratum corneum* and alters the skin microbiome, and UVA can induce PIH on acne skin, especially in dark skin types as well as very severe inflammatory acne.[20]

PIH treatments

Different treatments help to manage PIH. The response to treatment differs according to each treatment. A published review of 41 studies representing 877 patients mainly presenting with AI-PIH reported that complete response to treatment was obtained with laser and energy-based devices (18.1%), topical treatments -5.4%) and with combination therapies (2.4%). The prevalence of partial responses was much higher with 84.9% for combination treatment modalities, 72.4% with topicals, 61.2% with laser and energy based devices and 33.3% with peelings.[2] In 2017, a PIH treatment algorithm was proposed for the first time (Figure 2).[21] The authors suggested that for the treatment of epidermal PIH, triple combination (OD/8 weeks), topical retinoids (OD/12-18 weeks) or hydroquinone 4% (BID/12 weeks) may be indicated as first line treatments. As an alternative, niacinamide 4% (BID/ 9 weeks), azelaic acid 15% (BID/16 weeks), kojic acid, alpha hydroxy acid or botanicals may be proposed. Second line treatment includes glycolic acid peels every 3 weeks, starting at 50%, or salicylic acid peels every 2 weeks, starting at 20-30%. Management of dermal PIH requires 1064-nm QS Nd:YAG laser with low fluence or 1550-nm erbium-doped laser, while mixed PIH may require treatment for epidermal PIH, followed by a laser or energy-based procedure. AI-PIH may profit from topical treatments including retinoids (OD/12-18 weeks), azelaic acid 15-20% (BID/16/24 weeks) or hydroquinone 4% (BBID/12 weeks), and salicylic acid peeling (starting 20-30%/every 2 weeks). Several oral PIH treatment options have currently been suggested for off label use. These treatments

Figure 1 - PIH and predisposition in dark skin (phototype III to VI)

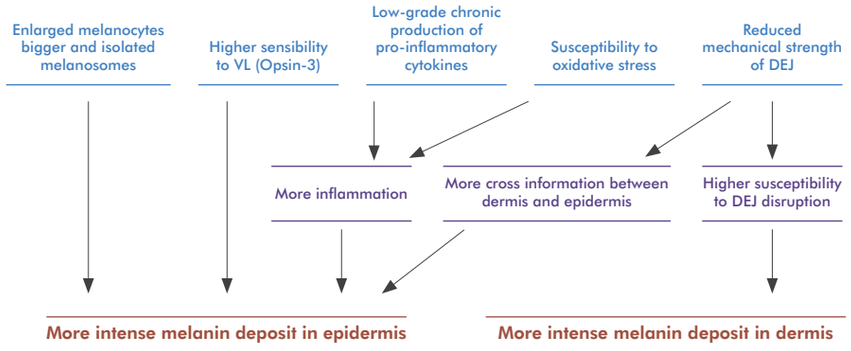
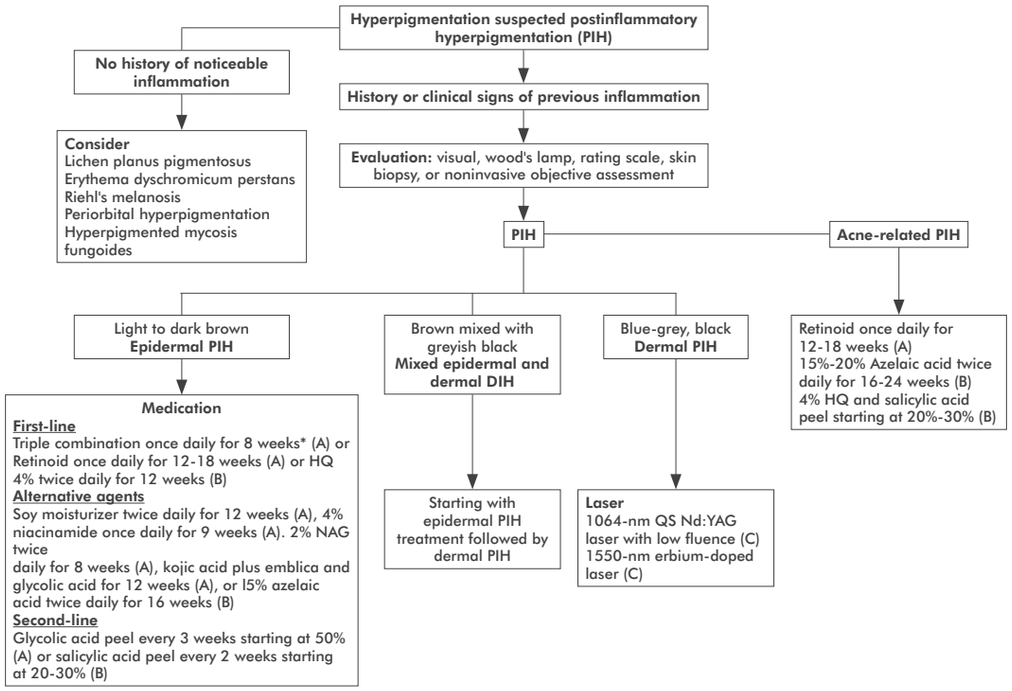


Figure 2 - Algorithm for the diagnosis and treatment of postinflammatory hyperpigmentation[21]



Broad-spectrum sunscreen and sun avoidance should be advised in all cases (B). The treatment should be changed or combined with other treatments after using current treatment with appropriate time and the patient considered that hyperpigmentation does not reach the patient's satisfaction.

Grade practice recommendation: (A) Strong recommendation (good evidence to support the use of the procedure: RCT), (B) Recommendation (fair evidence to support the use of the procedure: without RCT). (C) Option (poor evidence to support the use of the procedure: case series).

**Based on the evidence of melasma treatment.*

include tranexamic acid, French maritime pine (Pycnogenol®) and *Polypodium leucotomos* extract.[22] Tranexamic acid is a plasmin inhibitor, used to reduce blood loss caused by abnormal fibrinolysis. In PIH and hyperpigmentation it is suggested that tranexamic acid inhibits the UV-induced plasmin activity in keratinocytes, leading to a reduction of free arachidonic acid and prostaglandins, and decreased melanocyte tyrosinase activity. Pycnogenol® is an extract derived from the bark of the French maritime pine. It has antioxidant and anti-inflammatory properties. *Polypodium leucotomos* extract is a topical fern, native to Central and South America. It possesses strong antioxidant and anti-inflammatory activities after UV exposure. Studies have shown that it increases the minimal pigmentary dose, that it is effective as an adjuvant in melasma, and that it may reduce pigmentation caused by visible light.[23-25]

New topical treatments include cysteamine, bakuchiol and thiamidol, as well as topical tranexamic acid and depigmentation agents.[26] Cysteamine is a thiol that naturally occurs as a degradation, and its use can be limited by its malodor. However, studies have shown its benefit in melasma and a case-report in PIH.[27] Bakuchiol is a phytoactive that possesses functional properties similar to those of retinol. It has shown promising results in acne-induced PIH.[28] Thiamidol has been shown to be effective in acne-induced PIH.[29]

Prevention remains key in PIH. In acne-induced PIH, suitable photoprotection and treatment at early stages are strongly advised. In 2021, Passeron *et al*. proposed recommendations according to each phototype and dermatosis.[20] Organic UV filter sunscreens with a water or light liquid base and non-greasy textures have higher cosmetic acceptability and lead to better adherence for acne-prone skin. **Tinted sunscreens reduce visible light transmission twice as much as non-tinted sunscreens. The SPF value is less relevant than the presence of iron oxide for protection against visible light.**[20, 30]

Prior to any dermatological procedure, photoprotection is recommended for at least 2 weeks, and at least 2 weeks (maximum 1 month) after the procedure or until inflammation has resolved. Opaque dressing is the best option, whenever possible.

A sunscreen with an SPF 50+, high UVA protection (SPF/UVA-PF ratio as close to 1 as possible) and a (high energy) visible light photoprotection with tinted sunscreen should be recommended in skin type III or above.[20]

The risk of post-procedure PIH may be reduced by selecting the correct treatment according to each phototype, using low fluence on higher phototypes, avoiding ablative procedures on previously tanned skin and, of course, by using photoprotection.[30]

The patient's safety always comes first. A PIH risk assessment may be useful in addition to the Fitzpatrick skin phototype classification, and by asking the patients about their reaction to their skin after sun exposure rather than by a visual assessment of the skin tone, hair and eye color.[31] The assessment of sun reaction is based on a self-administered questionnaire in which the patients grade their erythema sensitivity and tanning ability, respectively.[32] Moreover, identifying previous signs of PIH, such as previous procedure marks and scars may be helpful to determine the most suitable treatment.[30]

Conclusion

PIH is a common pigmentary dermatosis in phototypes III and above. It has an important emotional impact on patients. Exposure to sunlight is recognized as a worsening factor. Therefore, early prevention by regularly applying sunscreens with a SPF50+ on sun-exposed areas of the body and early suitable treatment, especially in acne, are mandatory to limit the risk of PIH. Treatment should also depend on the type of PIH.

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LATEST NEWS IN MELASMA

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INTRODUCTION

Melasma is a mixed, chronic, acquired skin condition affecting both the epidermis and dermis. It is characterised by an overproduction of melanin in areas exposed to ultraviolet radiation.[1] Melasma usually appears as symmetrically located irregular macules and patches that are light brown to dark brown in color, developing mainly on the face (centrifugal, malar and mandibular), and less often on the neck and forearms.[2, 3]

Epidemiology and risk factors

Melasma occurs more frequently in women with darker skin complexions (skin phototypes III–V according to Fitzpatrick scale) in the third and fourth decade of life. A very recent article reports that melasma is also observed in 0.2% of men with a greater prevalence in dark skin phototypes.[5] **The global prevalence in Latin America varies between 9% to 30%.[6] in Mexico and Latin America, melasma figures among the five most frequently reported dermatoses, and is one of the main reasons for dermatology consultation in hospitals or in private practice.**

Risk factors include being a woman of phototypes III and IV, being of Asian or Latin American origin, or following viral infection. Moreover, hormonal factors such as oral contraceptives, pregnancy, genetic factors, chronic inflammation of the skin and prolonged exposure to solar radiation impact the etiopathogenesis and development of melasma.[4]

Assessment of melasma severity and impact on quality of life

Currently, melasma severity is evaluated using the melasma area severity index (MASI) and the modified MASI (mMASI); dermoscopy and confocal microscopy assess pigmentation changes in the epidermis and dermis.[7-10]

Melasma severely impacts the quality of life of patients resulting in a social and psychological burden. Several tools for measuring quality of life exist, such as the dermatological life quality index (DLQI), which is currently the most frequently used scoring tool in melasma protocols, as well as the melasma quality of life scale (MELASQOL).[11, 12]

Physiopathology

Melasma is characterised by the increased presence of biologically hyperactive melanocytes. One melanocyte maintains a connection with 36 keratinocytes to form an epidermal melanin unit.[13] In addition to the above-mentioned UVA, UVB also has a significant impact on the formation of hyperpigmentation, which stimulates keratinocytes to produce growth factors, including stem cell factor (SCF), basic fibroblast growth factor (bFGF), interleukin 1 (IL-1), endothelin 1 (EDN1), inducible nitric oxide synthase (iNOS), α-melanotropin (α-MSH), adrenocorticotropin (ACTH) and prostaglandin E2 (PGE2, dinoprostone). UV radiation stimulates mast cells which release histamine that plays a critical role in activating androgenesis when exposed to UV radiation.[4] UV radiation also stimulates mast cells to increase the production of tryptase.[14] An increase of tryptase leads to the damage of the basement membrane through the degradation of type 4 collagen.

At the keratinocyte and fibroblast level, a higher expression of cadherin 11 contributes to the damage of the basement membrane, with an increased migration of melanocytes deeper into the dermis observed.[15] These melanocytes are also known as pendulum melanocytes.[16]

Moreover, an increased expression of metalloproteinases 1 and 2 (MMP-1 and MMP-2) contributes to the degradation of the extracellular matrix, leading to the degradation of collagen and resulting in an accumulation of elastotic material in the skin.[15]

Senescent fibroblasts produce melanogenic growth factors, such as fibroblast stem cell factor and senescent-related protein 2 factor.[17]

Sebocytes play a significant role in the melanogenesis.[18] They secrete several cytokines including interleukin (IL)1α and IL6, which influence the synthesis of vitamin D, and produce growth factors that directly or indirectly modulate the melanocyte function.

Thyroid hormones are linked to melasma development.[19] A meta-analysis showed that serum levels of thyroid-stimulating hormone (TSH) and thyroid peroxidase antibodies (anti-TPO) have been found to be higher in patients with melasma, mainly in women.

The microbiome may also play an important role in melasma. Studies have provided evidence that patients with melasma have an increased cutaneous *Cutibacterium acne* load.[20, 21]

Treatment

Ultraviolet radiation is the most important risk factor. Broad spectrum sunscreens that provide protection against UVA, UVB and visible light, as well as an avoidance of sun exposure, remain the main preventive methods for melasma.

Currently, hydroquinone (HQ) containing products alone or in combination are the gold standard treatment in melasma.[22] The modified Kligman treatment has also been described as beneficial in melasma.[23] Other options include azelaic acid, glycolic acid alone or in combination, as well as topical tranexamic 5% to 10%, which is an emerging treatment for melasma, as well as niacinamide and kojic acid.[24-28] Invasive treatments include procedures, laser, chemical peels, microneedling, and intradermal injection of mainly tranexamic acid, as well as platelet-rich plasma injection and microdermabrasion. Superficial chemical peels or medium chemical peels can be combined with some of these invasive techniques, such as laser.[13, 29-31]. Moreover, oral tranexamic acid combined with a triple combination has been shown to be beneficial in melasma.[32]

Recently, a melasma treatment algorithm was published for Latin America that may allow health professionals to provide better treatment recommendations and help educate the patients.[6]

Conclusion

Knowledge about melasma has significantly evolved over the last few years, leading to new diagnosis and treatment approaches. To date, a multimodal approach integrating different methodologies may help to improve treatment. Clinical research continuously provides new insights, and emerging treatments provide new therapeutic options in melasma which may all allow to provide improved care for patients suffering from this condition.

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LASER AND INTENSE PULSED LIGHT: PIGMENTATION, PHOTO-REJUVENATION AND MORE

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INTRODUCTION

Before treating hyperpigmentation lesions or macules using laser or laser-and-energy based devices (EBDs), it is important to confirm that lesions are not at any risk to melanoma i.e. naevus or Dubreuilh melanoma. If any doubt persists, a dermoscopy, optical coherence tomography or histology examination should be performed.[1, 2]

Hyperpigmentation treatment

The best way to treat hyperpigmentation remains prevention, by protecting the skin from sun radiation.

For many years, cryotherapy was considered the treatment of choice for hyperpigmentation macules. However, it may also cause hyper- or hypo-pigmentation.[3] Currently, laser and EBDs are considered first line treatment in hyperpigmentation lesions, except in melasma, as they are effective and safe, with a rapid treatment outcome with crusts appearing after 3 to 5 days post-treatment.

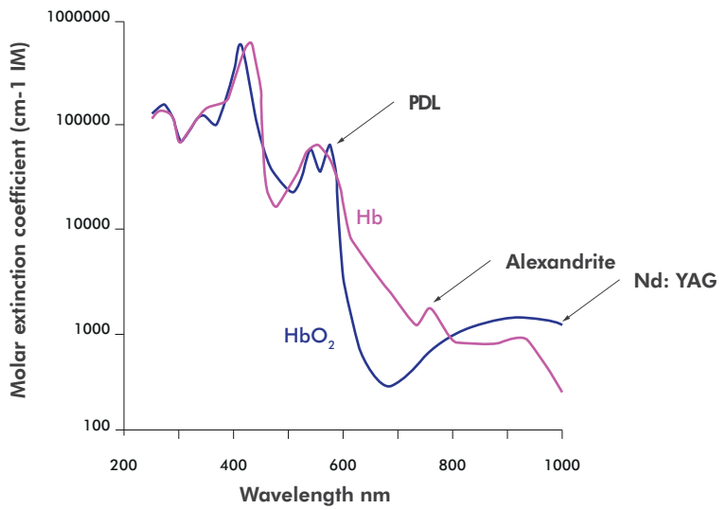
To treat solar lentigines, intense pulsed light (IPL), Q-switched nano and pico laser, with a low risk to hypochromia, as compared to cryotherapy, as well as fractional and radiofrequency laser, may be considered the most suitable treatments. Conversely, Alexandrite laser (735 nm), pulsed dye laser (PDL, 595 nm), and KTP (green light laser, 532 nm) should be considered with caution in these types of hyperpigmentation macules.[4]

IPL is effective in treating hyperpigmentation macules and telangiectasia. However, IPL also requires the selection of specific filters, treatment duration, number of pulses and, potentially, an associated cooling system. Moreover, it has low photo-selectivity and may cause burning, and, when using an older IPL version, cause a "Zebra" effect requiring a second treatment course.[5, 6]

To date, Q-switched nano and pico lasers are considered the gold standard procedure for photo-rejuvenation as they have a low depigmentation risk and a high rejuvenation effect. Due to their capacity of providing a selective photo-thermolysis, they disperse melanin by breaking up the melanin molecule without penetrating the deep skin layers, or causing burning or achromy. In solar lentigines, the use of Q-switched laser also allows the scanning of the macules leading in a precise treatment of each of them prior to treatment. Q-switched lasers are effective after 1 or 2 sessions, 2 months apart, and also improve skin texture and tone. They cause crusts within 8 to 10 days, and require sun protecting measures for one month post-treatment. [7, 8]

Vascular lasers include KTP, Nd Yag (16064 nm, long pulse waves), PLD and Alexandrite laser (Figure 1). When used in solar lentigines, KTP should be used in lesions of no more than 5 mm in diameter. PLD should be used concomitantly with a compression and without a cooling system. The use of Alexandrite laser allows the treatment of solar lentigines of up to 12 mm within 2 to 3 sessions, and the concomitant use of a cooling system.

Figure 1- Benefit of vascular lasers



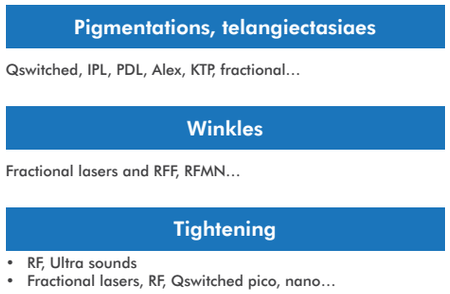
Fractional lasers and EBDs should not be used to treat large skin surfaces for post-surgery hyperpigmentation. Instead, limit treatment to small areas. Treatments can be ablative (photo-vaporisation) or non-ablative (photo-coagulation). These treatments can be applied using different wavelengths, radio frequences, and with or without microneedles. [9, 10] Non-ablative lasers are effective at 1440, 1540, 1550 and 1565 nm, and allow for a remodeling effect. Non-ablative fractional laser can be adjusted for its power, fluency and penetration, as well as for its mode of delivery and density.[11, 12]

A study using fractional 1550 nm erbium diode fiber non-ablative laser in 9 patients with bilateral moderate hand photodamage showed a significant improvement or better (23%) in the overall photodamage at the 6-month follow-up visit. Histological evaluation showed a reduction in atypical keratinocytes, improvement in rete ridge formations, increased collagen density and a reduction in solar elastosis at 6 months post-treatment.[13] Other results showed that this type of treatment was effective on dyschromia, wrinkles and skin texture.

Ablative fractional laser therapy comprises CO_2, erbium and radiofrequency laser. The parameters of this type of laser can be proportionally adjusted to the desired penetration, the lesion size, mode of impact delivery, density (i.e. the percentage of the surface to be treated), aggressiveness of the treatment and duration of pulse. Using a specific skin repairing cream may reduce crust disappearance to 3-5 days post-procedure. Fractional CO_2 ablative laser is not only beneficial in hyperpigmentation but also in post-inflammatory hyperpigmentation (i.e. in acne), acne scars, skin texture and tightening, as well as telangiectasia. Mono- or bipolar radiofrequency energy directly penetrates the skin tissue up to 5 mm using very fine microneedles.[9, 14] To increase the delivered energy, radiofrequency can be divided by multiplying the electrodes, thus inducing a fractional radiofrequency effect.

To allow for a complete skin rejuventation effect, including the treatment of hyperpigmentation macules, telangiectasia, wrinkles and skin tightening, different laser procedures can be combined (Figure 2). For example, to treat hyperpigmentation, the patient may first undergo vascular laser, IPL, Q-switched Yag or pico laser. To tighten the skin, bi- or multi-polar radiofrequency at a fluence of 60 to 100 J/cm², and to improve the skin texture fractional CO_2 laser, may be used. To obtain visible results, 3-5 treatments with a one-month interval between each treatment course should be respected.

Figure 2 - Ideal skin rejuvenation protocol using laser, radiofrequency and EBD devices



Laser treatment perspectives

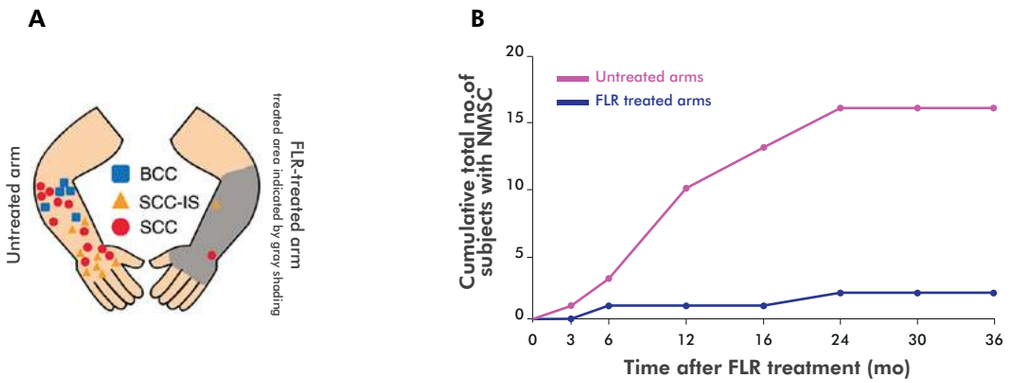
Laser treatment may not only be limited to skin rejuvenation or pigmentation issues. Several studies have confirmed that laser treatment also may be beneficial as prophylaxis against different types of non-melanoma skin cancer and carcinoma.

A randomised comparative trial showed that fractionated laser resurfaces on aged skin had **a positive effect against actinic neoplasia by eliminating senescent fibroblasts.**[15] The authors showed that a single treatment was durable in restoring appropriate UVB response in geriatric skin for at least 2 years, and in a sustained reduction in numbers of AKs and significantly decreased number of non-melanoma skin cancers in the treated arm (2 cases) *versus* the untreated arm (24 cases) after 3 years (Figure 3).

Another study showed that non-ablative fractional laser treatment is associated with a decrease risk of subsequent facial keratinocyte carcinoma (KC).[16] In this study, 43 non-ablative laser-treated patients with a history of facial KC and 52 matched control subjects were included. The rate of subsequent facial KC development was 20.9% in non-ablative laser-treated patients and 40.4% in control subjects (RR 0.52, p =0.049). Control subjects developed new facial KC significantly sooner than NAFL-treated patients (p=0.033). When controlling for age, gender, and skin type, control subjects were more likely to develop new facial KC than non-ablative laser-treated patients (hazard ratio 2.65, p=0.0169).

A final study showed that repeated exposure to fractional CO_2 laser delays squamous cell carcinoma formation and prevents clinical and subclinical photodamage, visualized by line-field confocal optical coherence tomography and histology.[17]

Figure 3 - Fractionated laser resurfacing reduces the occurrence of BCC and SCC in geriatric skin[15]



(A) Graphic representation of the location of BCC, SCC-*in situ*, and SCC identified on FLR-treated arms (n = 2) and untreated arms (n = 24).
(B) The accumulation of verified NMSCs occurring on untreated and FLR-treated arms.

Conclusions

To treat lentigo, IPL, Q-switched nano or pico laser may be considered the best choice. However, fractional treatments may also be associated to improve the skin texture, telangiectasia and other pigmentation issues. Laser treatment may help to prevent photodamage and has recently been shown to decrease the risk of the development of keratinocyte carcinoma. Future investigations on all available photo-rejuvenation technologies are necessary to assess their action on fibroblasts, their preventive effect on actinic keratoses, and on the prevention of non-melanoma skin cancer.

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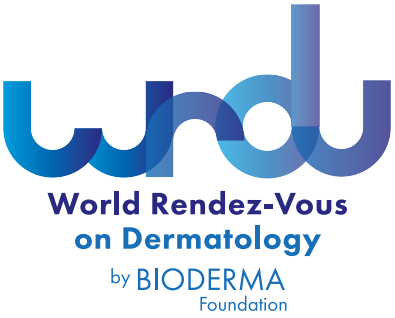
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