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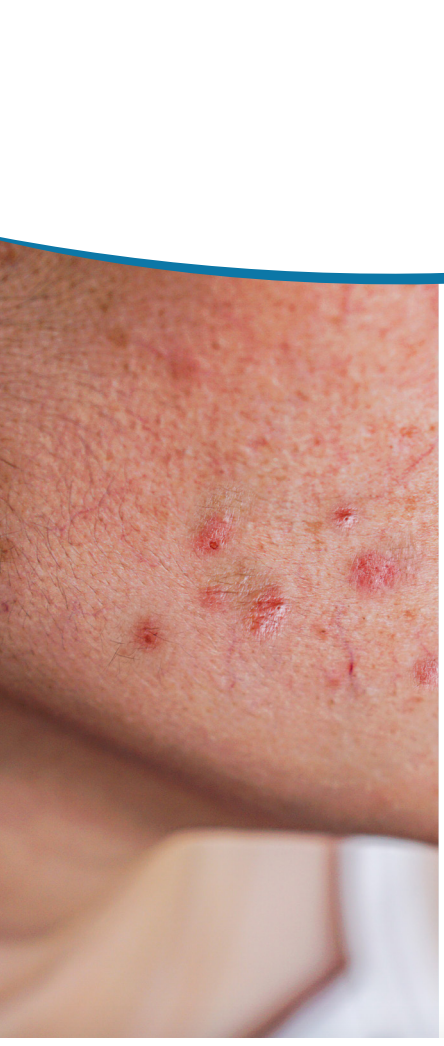
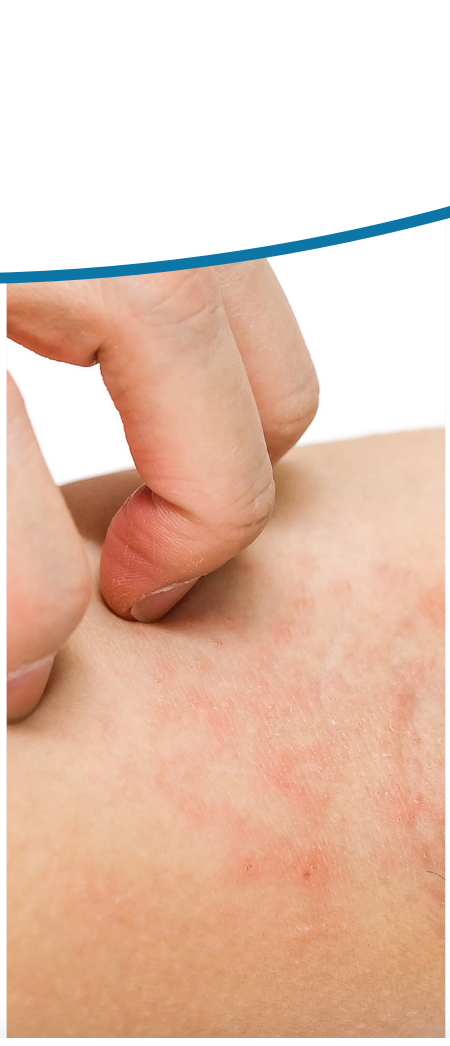
LABORATOIRE DERMATOLOGIQUE

UPDATES ON DERMATOLOGY

SKIN DISORDERS





ECOBIOLOGY AT THE SERVICE OF DERMATOLOGY

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EDITO

Stéphane FAUVERGHE
NAOS International Medical Director

Dear All,

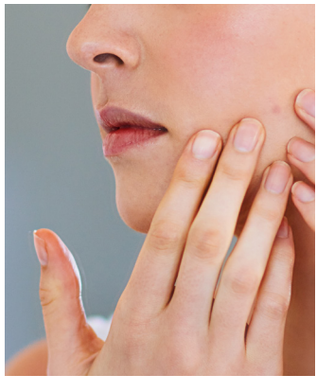
I am very pleased to present you the fourth edition of BIODERMA Updates Series dedicated to updates in Dermatology.

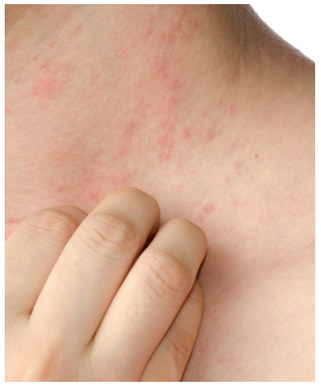
For 3 years now, BIODERMA has been regularly organizing international events dedicated to Dermatology, for dermatologists and all healthcare professionals interested in Dermatology, always presented by renowned experts in their field. In our approach to promote the development of knowledge in Dermatology, we have the pleasure to propose you this new publication that is the summary of the BIODERMA Symposium held during the EADV meeting in Milan in September 2022: **Dialogue around skin and its ecosystems** *with Prof. Brigitte DRÉNO from France, Prof. Enzo BERARDESCA from Italy, and myself as speakers.*

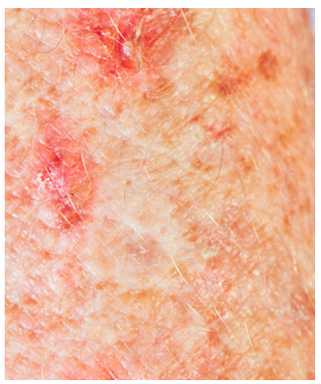
During this symposium, Brigitte DRÉNO presented the key updates on the microbiome, Enzo BERARDESCA delivered a lecture on the interactions between the skin barrier and environment and finally I presented how to act on the skin barrier to restore patients' quality of life.

I wish you all an enjoyable, enriching and interesting reading.

SUMMARY







SPEAKERS'S SHORT BIOGRAPHIES

Enzo BERARDESCA
USA

Enzo BERARDESCA is director of the dermatology department of inflammation and immuno-infectiousness at the Institut de dermatologie de San Gallicano, IRCCS, Rome. He has published more than 400 scientific books and 8 books. From a scientific point of view, he has been involved for many years on the integument, using non-invasive methods to conduct efficacy and safety studies on topical products. He is scientific director of Dermakos magazine.

Enzo Berardesca, obtained his training at the University of Pavia and received the M.D. degree in 1979. He served as resident and dermatologist in the Dept of Dermatology, IRCCS Policlinico S. Matteo, Pavia from 1982 to 1987, as research assistant in the Dept. of Dermatology, University of California School of Medicine in San Francisco, USA in 1987.

From 1988 to 2001 he has been at the Dept. of Dermatology of the University of Pavia, head of the Dermatoallergology Unit and of the Skin Bioengineering Lab.

He is member of the editorial board of Skin Pharmacology, Skin Research and Technology, The American Journal of Clinical Dermatology and the Journal of Cutaneous and Ocular Toxicology. He is member of the Society for Investigative Dermatology, the European Society for Dermatological Research, the Italian Group for Research on Contact Dermatitis (GIRDCA), and vice-chairman of the European Group For standardization of Efficacy Measurements of Cosmetics (EEMCO group).

His current major research interests are irritant dermatitis, barrier function and noninvasive techniques to investigate skin physiology with particular regard to skin color and racial differences in skin function, sensitive skin and efficacy evaluation of topical products.

Brigitte DRÉNO
France

Prof. Brigitte DRÉNO is a Dermato-Oncologist. She is also Vice President to the Scientific and technical Culture of Nantes University France. She leads a research project included in the investments for the future hospital-university research in health (RHU) focusing on burn and regenerative dressing. She works also the field of melanoma, drug-induced cutaneous adverse events and microbiome and acne. She is the director of an INSERM INCITE research team.

She is Founding member of the European Association of Dermato Oncology (EADO), past president of the French Society of Dermatology and French college of dermatology teachers, Treasurer of the International League of Dermatological Societies (ILDS). In addition, member of AAD, ADA, International Society for Cutaneous Lymphomas, Skin Cancer Foundation. She has published over 900 articles referenced in PubMed (H Index 83), participated to the redaction of chapters of several books. She built the first GMP cell and gene therapy hospital unit in France in Nantes.

She is an Editorial Board Member of JEADV, Acta Dermatology, European Journal of Cancer Prevention, International Journal of women's Dermatology and Editor of the quarterly medical review (La Presse Médicale). She has obtained several awards such as the Award of ILDS, the Prize of the International Society for Cutaneous Lymphomas, the Prize of the French victories of medicine. She has been granted to the grade of Knight of the Legion of Honor by the President of the French Republic, as well as Chevalier in the Order of Academic Palms of Nantes' s University and has been elected recently member of the French Academy of Medecine.

DIALOGUE CONCERNING THE SKIN AND ITS ECOSYSTEM, KEY UPDATES ON THE SKIN MICROBIOME

BRIGITTE DRÉNO

Nantes Université, INSERM, CNRS, Immunology and New Concepts in ImmunoTherapy, INCIT, UMR 1302/EMR6001, *Nantes, France*

Foetal skin is colonized by microorganisms from the mother as early as birth.[1] Skin colonization by commensal skin microorganisms continues during breastfeeding.[2] In parallel, microorganisms from the environment attempt to colonize the skin and scalp, as well as specific areas such as the perigenital and perioral areas, and some succeed in building a healthy relationship with host skin cells. Thus, by adulthood a final state of equilibrium is acquired, with an astoundingly diverse commensal/mutualistic skin and scalp microbiota that is unique at a genus level for each individual.[3]

The balanced skin microbiota is comprised of resident microorganisms, which are a relatively stable group (the core microbiota) routinely found in the skin and which re-establish themselves after perturbation, and transient microorganisms that do not establish permanent residency, but which rather arise from the environment and persist for hours to days before disappearing. Under normal conditions, both groups are non-pathogenic.[4, 5] Any alteration of the natural skin barrier results in dysbiosis, an unbalancing of the microbiota, with an activation of the innate immunity and the risk of penetration in the skin of antigens, such as pathogen bacteria.

Grice *et al.* characterized four main resident phyla: *Actinobacteria*, *Firmicutes*, *Proteobacteria*, and *Bacteroides*. The 3 most common genera where: *Corynebacteria*, *Cutibacteria*, and *Staphylococci*.[6] Both the composition and abundance vary considerably between individuals and over time, resulting in an extremely dynamic and greatly fluctuating microbiota.[7, 8]

Habitats such as eccrine and apocrine glands, sebaceous glands and hair follicles, are likely to be associated with their own unique microbiota.[4, 9] Sebaceous sites have higher density of particularly lipophilic species, such as *Cutibacterium*, which has adapted to this lipid-rich, anaerobic environment.[10-13] The drier sites host predominantly *Staphylococcus*, *Micrococcus*, *Corynebacterium*, *Enhydrobacter*, and *Streptococcus* species.[14]

Many other types of organisms also reside on the skin, including *Malassezia* spp., a polymorphic yeast, sometimes classified as a fungus, present on most parts of the body, especially on the scalp and which accounts for 80% of cutaneous fungi, and demodex, a parasitic arthropod.[15, 16]

Demodex plays a major role in rosacea and *Cutibacterium acnes (C. acnes)* in acne. In both diseases, natural skin barrier functions may be impacted by these residents, including the stratum corneum lipidic film, as well as anti-radical, immune, thymic and endocrine functions. This dysfunction may result in hyperseborrhoea or dysseborrhoea, vascular hyperreactivity and impaired alkaline metalloproteases.

Acne and rosacea, despite their similar clinical presentations, follow distinct clinical courses, suggesting that fundamental differences exist in their pathophysiology. A case-control study profiled the skin microbiota in rosacea and acne patients compared to matched controls. Results showed that the mean relative abundance of *C. acnes* in rosacea with inflammatory papules and pustules *(20.5% ±16.9%)* was more similar to that of acne *(19.1% ±15.5%)* than that of rosacea without inflammatory papules or pustules *(30.4% ±21.9%)*. *C. acnes (p=0.048)* and *Serratia marcescens (p=0.038)* were significantly enriched in individuals with rosacea compared to acne. Investigating the differences between the skin microbiota in acne and rosacea can provide important clues towards understanding the disease progression in each condition.[17]

Rosacea triggers cause the activation of downstream effectors *(i.e. PAR2, TLR-2,, LL-37, inflammosome, TSLPTRPA1 and TRPV4)* in various cell types such as keratinocytes, macrophages, neutrophils, fibrolasts and mast cells, probably by the activation of a few specific receptors and channels, which in cooperation nurture processes of inflammation, including oedema and vasodilation, fibrosis, pain, and angiogenesis. For example, epidermal and probably immune cell-expressed proteinase-activated receptor-2 *(PAR 2)* and Toll-like receptor-2 *(TLR-2)* are activated by rosacea-associated bacterial and Demodex-derived proteases, leading to the induction of the inflammasome and subsequent release of pro-inflammatory agents, such as tumour necrosis factor-alpha *(TNF-α)* and interleukin-1 *(IL-1)*, as well as the enhanced expression of the innate immune peptide LL-37. ATP, adenosine triphosphate; CGRP, calcitonin gene-related peptide; ET1, endothelin-1; ETAR, endothelin A receptor; KLK-5, kallikrein-5; LL-37, cathelicidin; MMP, matrix metalloproteinase; NALP3, NACHT, LRR, and PYD domain-containing protein 3; PACAP, pituitary adenylate cyclase-activating peptide; SP, substance P; TGF-β, transforming growth factor-beta; TRP, transient receptor potential; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor.[18]

Acne is a multifactorial, potentially chronic and inflammatory disease that mainly starts during puberty. At that period of life, over-colonisation of the pilosebaceous unit by *C. acnes* leads to a loss of diversification and dysbiosis, potentially being the cause of acne.[19-24] Research has shown that aloss of diversity of *C. acnes* phylotypes, following a selection of phylotype IA1/CC18 present in all acne patients, may worsen the condition.[25-27] Different inflammatory profiles, depending on the phylotype (*i.e.* phylotype IA1, which has mainly been observed on the face and back of acne patients, and cluster of *C. acnes* activating the innate immunity *via* the expression of protease activated receptors *(PARs)*, tumour necrosis factor *(TNF-α)*, and the production of interferon *(INF-γ)* and interleukins *(IL-1β, IL-8)*, have been observed.[25, 28-36] Moreover, besides causing dysbiosis, *C. acnes* also activates the release of lipases, matrix metalloproteinases *(MMPs)* and hyaluronidases, leading to hyperkeratinisation of the pilosebaceous unit and finally to comedones, papules and pustules.[28-31, 37]

Staphylococcus epidermidis (S. epidermidis) is the most frequently isolated commensal species from human epithelia.[25, 39] *S. epidermidis* is able to inhibit *C. acnes*-induced inflammation. This may be due to the staphylococcal LTA-induced miR-143 on keratinocytes, known for limiting inflammation. Research has suggested that the mechanism for LTA-miR-143-mediated suppression of TLR2 signalling is accomplished by miR-143 targeting 3'UTR of TLR2. It thereby decreases the TLR2 protein production, which plays a major role in the inhibition of *C. acnes*-induced cutaneous inflammation.[38-40] Thus, it helps to regulate skin homeostasis and to suppress the pathogenic inflammation that is induced by *C. acnes*.[39, 41]

Accordingly, an unbalanced equilibrium between *C. acnes* and *S. epidermidis* in the pilosebaceous units of acne patients in favour of phylotype IA1 CC18 *C. acnes* strains (75-80 of cases) may not allow *S. epidermidis* to fully play its role as a regulator of the natural skin homeostasis in limiting the growth of *C. acnes*.

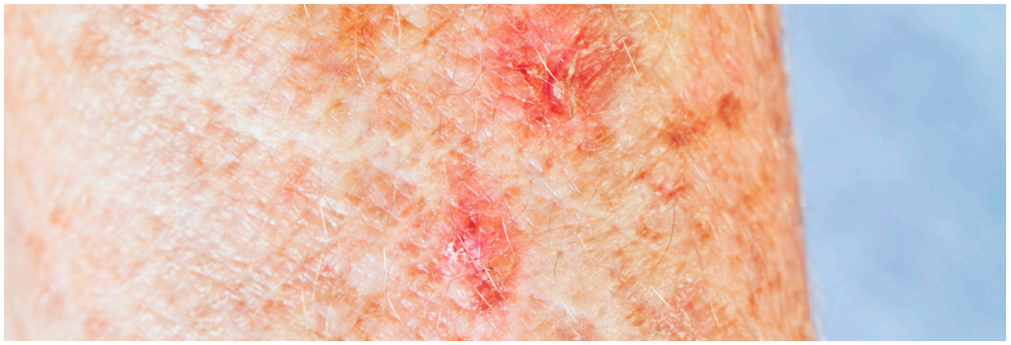
However, the commensal microbiota does not only play a role in the skin homeostasis - it may also play a role in skin cancer.

The cancer microenvironment has recently been recognized to be able to modulate cancer progression and treatment response. One of these cancer microenvironments is the human microbiome. Among the estimated ~1012 distinct microbial species on earth, 11 are labelled human carcinogens, or "oncomicrobes," by the International Association for Cancer Registries *(IACR)*. These oncomicrobes cause an estimated 2.2 million cases per year *(~13% of global cancer cases)*.[42] Among these oncomicrobes figures *C. acnes*, which may potentially trigger bladder and prostate cancers.

Other research has shown that the pathogen *S. aureus* is strongly associated with both actinic keratoses *(AK)* and squamous cell carcinoma *(SCC)*.[43-45] *S. aureus* secretes a virulent peptide called modulin which induces the secretion of IL-1, IL-6 and TNF-α which, in turn, activate TH17 cells and T Regs with a release of IL-17. IL-17 with IL-22 regulates the cutaneous colonization of *S. aureus* by triggering a self-maintenance inflammation mechanism. Moreover, *S. aureus* overgrowth in SCC is associated with a highly increased hBD-2 level, which may play a role in the maintenance of chronic inflammation. Krueger *et al.* described the cytokine profiles secreted by *S. aureus* in AK and SCC for the first time. *S. aureus* induces a chronic pro-inflammatory environment in the skin, which may have important consequences in the treatment of AK and the prevention of SCC.[43]

Conversely, *S. epidermidis* does not only limit inflammation in acne caused by *C. acnes*, it has also been shown to protect against skin neoplasia.[46] *S. epidermidis* strains produce 6-N-hydroxyaminopurine *(6-HAP)*, a molecule that inhibits DNA polymerase activity. In culture, 6-HAP selectively inhibited the proliferation of tumour lines but did not inhibit primary keratinocytes. Resistance to 6-HAP was associated with the expression of mitochondrial amidoxime reducing components, enzymes that were not observed in cells sensitive to this compound. Intravenous injection of 6-HAP in mice suppressed the growth of B16F10 melanoma without evidence of systemic toxicity. Colonization of mice with an *S. epidermidis* strain producing 6-HAP reduced the incidence of ultraviolet-induced tumours compared to mice colonized by a control strain that did not produce 6-HAP.

These findings suggest that commensal bacteria of our skin microbiota may be able to suppress tumour growth and thus protect the body against skin cancer, with dysbiosis being detrimental to the body defence because of a loss of the protective function of certain commensal bacteria.



IN CONCLUSION

The beneficial and protective role of the commensal bacterial community of our body is not limited to inflammatory diseases but also extends to cancer, including that of the skin. Understanding the skin microbiome is at a turning point and developing microbial-derived products with bioactive activities on the microbiota may be an important issue to consider in the future.

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INTERACTIONS BETWEEN THE SKIN BARRIER AND THE ENVIRONMENT

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The skin barrier including the *stratum corneum (SC)* constitutes the first line of physical, chemical, and immunologic defenses providing a protective wall against environmental factors, excessive transepidermal water loss *(TEWL)* and skin dryness.[1] The SC is mainly composed of corneocytes linked by corneodesmosomes. The intracellular space is made by lipid lamellae and various proteins forming the mortar. Environmental threats to the skin include UV radiation *(almost 90% of causes)*, cigarette smoke, ozone, aldehydes produced through the interaction between ozone and smoke exposure, ozone and UV radiation as well as airborne pollutants by industry and central heating.[2] Ozone mainly acts on the SC. In contrast, organic compounds present on the surface of particulate matter *(PM)* may penetrate into skin and act on viable skin cells such as keratinocytes and melanocytes, *e.g.* by binding to the aryl hydrocarbon receptor *(AhR)*, resulting in gene expression relevant for skin ageing and pigmentation and to oxidative stress causing skin inflammation.[2]

PM induce oxidative stress *via* the production of reactive oxygen species *(ROS)* and secretion of pro-inflammatory cytokines such as TNF-α, IL-1α, and IL-8. The increased production of ROS such as superoxide and hydroxyl radical by PM exposure increases MMPs including MMP-1, MMP-2, and MMP-9, resulting in collagen degradation, leading to inflammatory skin diseases and skin ageing. Moreover, ultrafine particles *(UFPs)* including black carbon and polycyclic aromatic hydrocarbons *(PAHs)* increase the incidence of skin cancer. Overall, increased PM levels are highly associated with the development of various skin diseases *via* the regulation of oxidative stress and inflammatory cytokines.[3]

The impact of airborne pollutants was assessed for the first time by Vierkötter *et al.* in 2010. **Results showed that air pollution exposure significantly correlated to extrinsic skin ageing signs, especially to pigment spots and, less pronounced, to wrinkles.** An increase in dust and traffic particles was associated with 20% more pigment spots on forehead and cheeks. Background particle pollution was also positively correlated to pigment spots on face.[4]

In vitro and *in vivo* experiments in pigs assessed the responses of the skin to PM. PMs primarily containing heavy metals *(1648a)* and polycyclic aromatic hydrocarbons *(PAHs, 1649b)* were applied on the skin. According to the transepidermal water loss *(TEWL)*, 1649b but not 1648a significantly disrupted the SC integrity by 2-fold compared to the PBS control. The immunohistochemistry *(IHC)* of cytokeratin, filaggrin, and E-cadherin exhibited that 1649b mildly damaged tight junctions. The cytotoxicity of keratinocytes and skin fibroblasts caused by 1649b was stronger than that caused by 1648a. The 1649b elicited apoptosis *via* caspase-3 activation. Proteomic profiles showed that PM upregulated Annexin A2 by >5-fold, which thus can be used as a biomarker of PM-induced barrier disruption. The skin uptake of ascorbic acid, an extremely hydrophilic drug, was increased from 74 to 112 µg/g by 1649b treatment and the extremely lipophilic drug tretinoin also showed a 2.6-fold increase of skin accumulation confirming that drug absorption may be increased in damaged skin. The *in vivo* dye distribution visualized by fluorescence microscopy indicated that 1649b intervention promoted permeant partitioning into the SC.[5]

A study conducted in Shanghai confirmed that TEWL and squalene as well as cutaneous lipid concentrations were considerably increased in skin of subjects living in urban areas compared to non-urban areas. Conversely, lactic acid and the D-squame index were significantly reduced *($p<0.05$)*. Pollution exposure especially heavy traffic pollution exposure was associated with a lower SC trypsin-like enzyme activity *(SCTE)*, reduced catalase activity and total antioxidant capacity *(TAOC)*. As a result, subjects from polluted areas had much more skin diseases and disorders reported.[6]

Pollution also increases the risk of melasma and other hyperpigmentation disorders.[7] PM and PAHs enter the skin *via* nanoparticles and generate quinones, which are redox-cycling chemicals that produce ROS. PM increase the amount of ROS, which triggers the increase of metalloproteinases, which leads to extrinsic aging, including skin pigmentation. The incidence of disorders of facial hyperpigmentation specifically, melasma, is increased in subjects of skin type III-VI.

As already stated above, urbanization and socioeconomic development led over the last decades to an increased exposure to air pollution, and chemical hazards increased the risk of a disruption of the physical integrity of the skin barrier by degrading the intercellular barrier proteins at tight and adherens junctions, triggering epithelial alarmin cytokine responses such as IL-25, IL-33, and thymic stromal lymphopoietin, and increasing the epithelial barrier permeability. As a result, a typical type 2 immune response develops in affected organs leading to asthma, rhinitis, chronic rhinosinusitis, eosinophilic esophagitis, food allergy, and atopic dermatitis *(AD)*. The damagaed skin barrier allows allergens to penetrate the skin leading to systemic sensitization.[8, 9]

During the last years, microplastic has become a more and more important health issue. **Microplastic particles have been shown to penetrate tissues and to interact with cellular structural molecules, to cause the proteins to fold and to alter their structure, to denaturate interact lipid bilayers, to alter cell membranes.** Moreover, they induce inflammatory gene transcription, pro-inflammatory cytokines, and pro-apoptotic protein expression and cause endoplasmic reticulum, mitochondrial dysfunction and induce cell death by oxidative stress.[1, 10-15]

AD is a chronic, inflammatory skin disorder which may serve as a model in skin barrier dysregulation. The increased understanding of the complex composition and functions of the epidermal barrier allows for a deeper appreciation of the active role that the skin barrier plays in the initiation and maintenance of skin inflammation. Not only lesional, but also non-lesional areas of AD skin display many morphological, biochemical and functional differences compared with healthy skin.[16]

In AD skin, filaggrin gene variants may lead to decreased natural moisturizing factor, which reduces *stratum corneum* hydration and increases pH.[17] Increases in pH enhance protease *(KLK5, KLK7 etc.)* activity and inhibit lipidgenerating enzymes.[18] 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.[18, 19] Genetic changes in cornified envelope *(e.g., FLG variants and SPRR3)*, lipid matrix *(e.g., TMEM79)* and tight junction *(CLDN1)* components are thought to impair the structural integrity of the cornified envelope and lipid lamellae.[17, 20-23] Tight junction defects and increased pH impair antimicrobial activity, increasing the probability of *S. aureus* infections, which then worsen the skin barrier breakdown.[24, 25] Environmental factors such as soap, detergents and exogenous proteases further enhance protease activity, interacting with genetic defects to break down the skin barrier.[26] Once the skin barrier is impaired, the penetration of irritants and allergens into the skin increases, triggering even further skin inflammation and raising protease activity. Thus, there is evidence that natural environmental allergens and man-made pollutants are associated with an increased likelihood of developing AD.[18, 24]

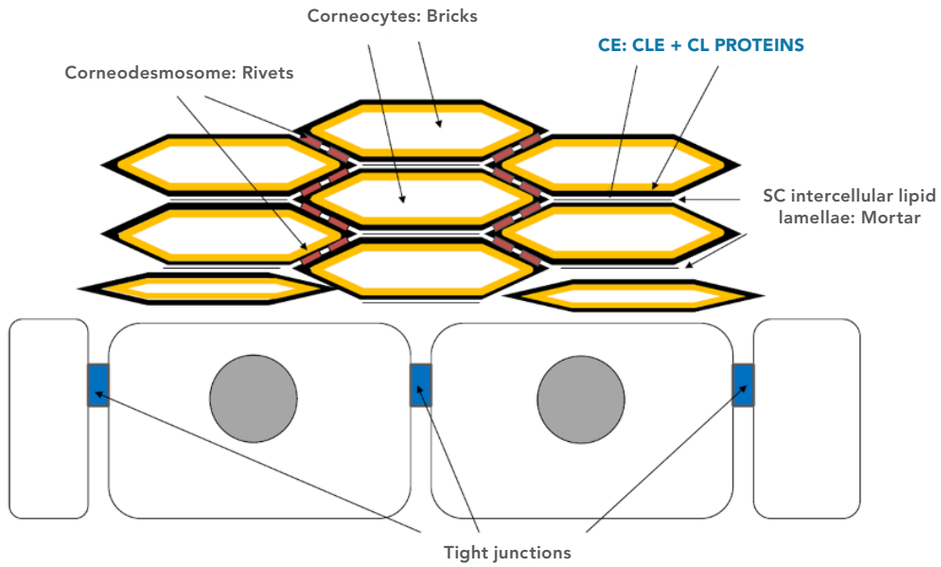

Figure 1. Healthy skin barrier

IN CONCLUSION

Maintaining the integrity of its barrier is important to maintain a healthy skin. In addition to UV radiation, many other external factors are detrimental to the healthy skin barrier. They trigger skin diseases and maintaining and, thus, repairing the skin barrier is not only a cosmetic but also a general health issue while protecting the environment in reducing pollution, will help to maintain a healthy skin barrier.

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ACTING ON THE SKIN BARRIER TO RESTORE PATIENTS' QUALITY OF LIFE

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In atopic dermatitis *(AD)*, the natural skin barrier is impaired *(Figure 1)*. As a result, the penetration of allergens into the skin is eased and transepidermal water loss *(TEWL)* increased due to a hydrolipidic film deficiency and an inadequate ceramides/cholesterol ratio. Moreover, the natural moisturizing factor *(NMF)* related to filaggrin deficiency and the natural microbial diversity are decreased, while an abnormal microbial colonization with biofilm-forming pathogenic organisms such as *Staphylococcus aureus (S. aureus)* during flares, compared to *Staphylococcus epidermidis* in healthy individuals, can be observed. The skin becomes increasingly susceptible to skin infection and inflammation.[1]

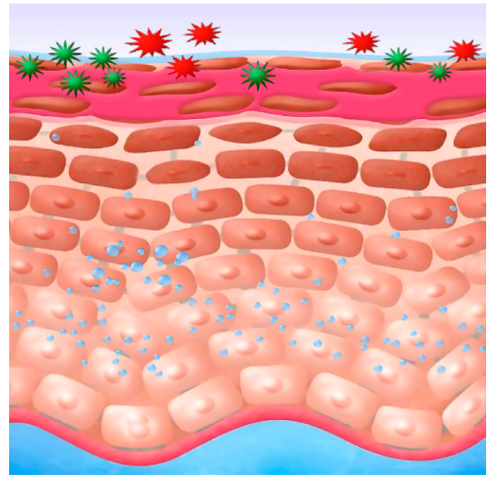


Figure 1. Impaired skin barrier

Biofilm is the dominant mode of growth of the skin microbiota. It promotes adhesion and persistence in the cutaneous microenvironment, thus contributing to the epidermal barrier function and local immune modulation. In turn, the local immune microenvironment plays a part in shaping the skin microbiota composition. During AD flares, the pathogen biofilm-growing *S. aureus* emerges as the major colonizer in the skin lesions, in association with disease severity *(Figure 2)*. The chronic production of inflammatory cytokines in the skin of AD patients concurs with supporting *S. aureus* biofilm overgrowth at the expense of other microbial commensals, leading to dysbiosis.[2]

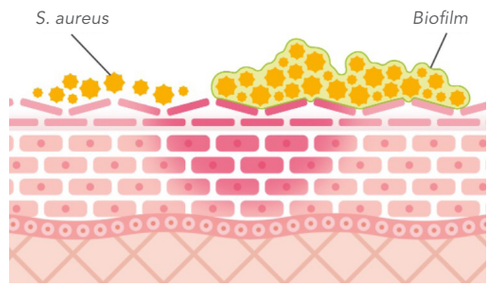
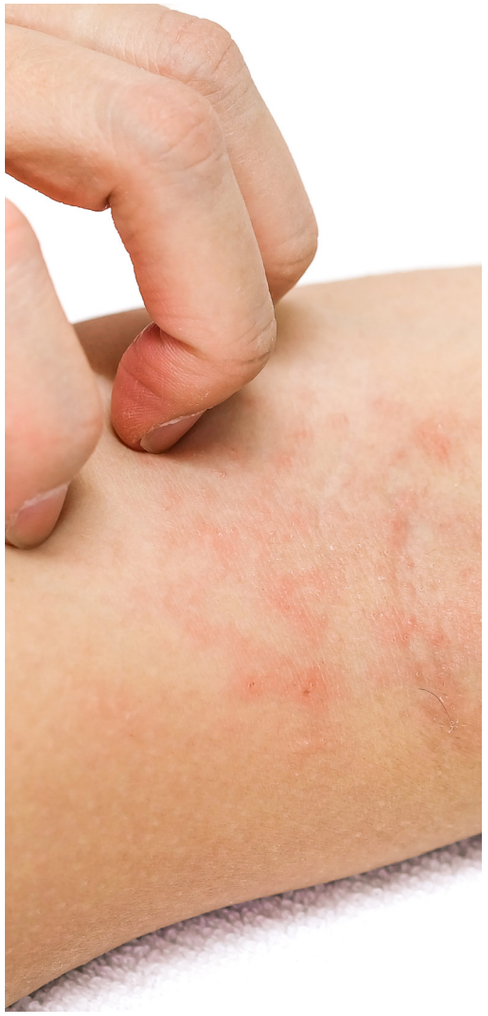


Figure 2. Staphyloccus aureus *colonization and biofilm formation in atopic dermatitis*



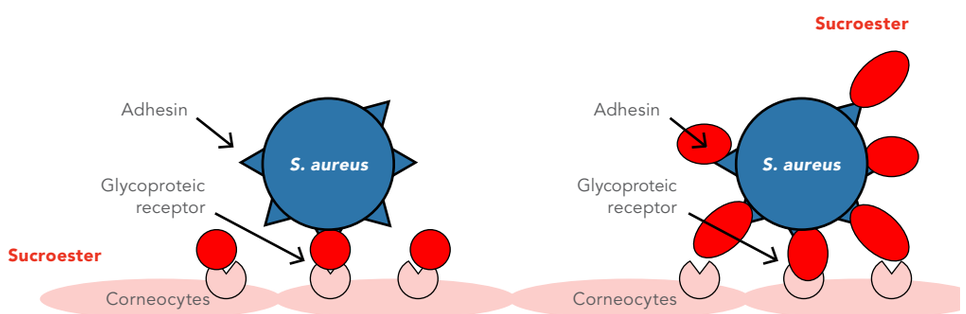
As a chronic disease, AD heavily impacts the patients' and families' quality of life, due to frequent scratching, decreased sleep efficiency, troubles getting to sleep, reduced total sleep time, and difficulties waking up in the morning. Moreover, patients may experience daytime drowsiness, irritability and other phenomena.[16, 17]

Current European and American guidelines recommend the regular use of emollients in addition to or as an alternative to adequate pharmacological treatment, in order to help reduce AD severity. Current AD treatment consists mainly of topical corticosteroids for milder and more moderate forms of AD, and biological therapies for more severe forms of AD, as well as emollients that may be used as a regular adjuvant or alone between treatment courses with corticosteroids. Emollients are essential in the management of AD through their action in helping to restore the healthy skin barrier and its microbiota. Emollients with a higher lipid content should be preferred and applied soon after bathing or showering to improve skin hydration.[3, 4] Their daily use in adequate amounts is strongly recommended to improve the patient course.[4-8] Despite their benefit, only one third of all AD patients comply with their topical treatment regimen and only half of them apply the recommended amount of emollients.[9, 10] **Thus, there is a need for education and for emollients that are efficacious, safe in all skin types and which have a suitable texture to sensorially increase compliance of use.**

NAOS is the pioneer in ecobiology, a unique scientific approach that uses the in-depth knowledge in skin biology to protect its ecosystem. By observing, understanding and mimicking the natural mechanisms of the skin, ecobiology favours biomimetic ingredients that help the skin to strengthen and replicate itself, and stimulates its natural rebalancing and regeneration mechanisms, thus balancing and regenerating itself.

Based on this ecobiological approach, NAOS has developed a specifically adapted emollient, Atoderm® Intensive Baume. This emollient contains phytosphinghosine *(Lipigenium™ complex)* that helps to restore the natural skin barrier by activating the neosynthesis of ceramides and restoring the neosynthesis of filaggrin.[11, 12] Unpublished research has shown that filaggrin expression increased by 37% after only 7 days of daily use of the emollient. It also contains biomimetic lipids, including Ceramide 1, 3 and 6, cholesterol, and different essential fatty acids to replenish the lipid barrier, as well as a sucroester *(Skin Barrier therapy™, SBT)* to limit adhesion and biofilm formation of *S. aureus*, while preserving the natural microbiome. *In vitro* studies have shown that SBT reduces *S. aureus* adhesion on human corneocytes by log -3 *(Figure 3, data on file)*. Moreover, the emollient contains palmitoyl ethanol amide *(PEA)* to reduce pruritus. PEA regulates pruritus by acting on TRPV-1, CB2, PPAR-α, and thus improves skin comfort and the patients' quality of life (data on file). [13-15]

Clinical studies have shown that the emollient significantly decreases the urge to scratch in 94% of patients, and durably stopped pruritus in 88% (p<0.001) after 21 days of use, with a significant onset immediately after application. Moreover, it significantly decreased the whole body SCORAD according to the dermatologist (p<0.05), as well as that scored by the patients or parents (p=0.0158), and improved the patients' quality of life (p<0.0337) after 168 days of daily use. One such study also showed that the time between relapses had increased and that the severity of relapses had decreased by 49%, with 76% of all patients not relapsing at all. Moreover, a strong correlation between the decreased *S. aureus* biofilm and the improved quality of life was observed (data on file). Not surprisingly, other clinical work confirmed that the daily use of the emollient by AD patients also significantly improved the families' quality of life. Overall, 84.8% of the parents were no longer affected by their child's AD, and sleep was no longer impacted for 86.4% of the patients (data on file).



Sucroesters limit the adhesion of pathogenic germs like *S.aureus* on skin.

Figure 3. Mechanism of the sucroster patented technology limiting S. aureus *adhesion on human corneocytes*

IN CONCLUSION

Due to its strong anti-inflammatory properties during AD flare-ups, the specifically developed Atoderm® Intensive Baume emollient supports the benefit of dermatological treatments by helping to clear flare-ups. Moreover, it supports the restoration of the natural skin barrier and is extremely well tolerated. Between AD flare-ups, it contributes to the regulation of pruritus and inflammatory response, helps to strengthen the natural skin barrier, and improves both the patients' and families' quality of life.

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NOTES

ECOBIOLOGY AT THE SERVICE OF DERMATOLOGY

Learn more about NAOS, French ecobiology company,
founder of BIODERMA, on www.naos.com

NAOS, SAS with a capital of € 43,474,650,R.C.S. Aix-en-Provence B535 236 418, 355 rue Pierre-Simon Laplace 13290 Aix-en-Provence. LL-BA (0226) May 2023