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Fixing the skin barrier: past, present and future – man and dog compared

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Skin barrier dysfunction exists in both human and canine atopic dermatitis, leading to increased water loss and potentially facilitating allergen penetration and sensitization. Both lipid (e.g. ceramides) and protein (e.g. filaggrin) abnormalities have been described. Some are genetically inherited (e.g. filaggrin mutations are one of the major risk factors in humans) and some are secondary and linked to inflammation.

In humans, numerous studies have shown efficacy of emollients and moisturizers in barrier restoration, and this approach has been for years the mainstay of therapy. Recently, this strategy has shown promise as a preventative function.

In veterinary medicine, evidence regarding skin barrier impairment is rapidly building. Decreased ceramides and filaggrin (in some subsets of dogs) have been described. Altered metabolism of ceramides has also been proposed. Despite these preliminary data and the availability of products marketed to improve the skin barrier, evidence regarding the clinical benefit of skin repair intervention is still limited. Preliminary studies have demonstrated that topical application of fatty acids and ceramides and systemic administration of fatty acids improve lipid deficiencies in the skin of dogs with atopic dermatitis, but limited clinical evidence exists.

Disease remission in humans is paralleled by an improved skin barrier, both with calcineurin inhibitors and glucocorticoids. In veterinary medicine, a preliminary study on ciclosporin and prednisone failed to detect significant improvement of water loss, while successful immunotherapy correlated with an improved skin barrier. Controlled, large studies are needed to address the question of which skin repair approach is clinically most effective and whether this can be used as a preventative strategy.

What is known in human medicine

The importance of addressing skin dryness in humans with atopic dermatitis (AD) has been known for decades. A direct relationship exists between skin dryness and disease severity in AD patients.[1] Both moisturizers and emollients have been shown to improve the skin barrier and clinical signs.[2] Skin barrier creams increase the time between flare-ups and reduce relapses by about one-third compared with no treatment.[3] Skin care has also a preventative function. Early implementation of emollient therapy (petrolatum based) decreases the frequency of development of AD in high-risk children to 15%, compared with 30–50% when no skin care is done.[4] Despite the fact that skin barrier repair has been practised for a long time, the debate on the best ingredient to use is ongoing.

Emollients, moisturizers and products based on lipids/ceramides: which one is the best?

The terms moisturizers and emollients are frequently used interchangeably, although moisturizers typically contain water as the main ingredient mixed with humectants to hydrate the stratum corneum, while emollients classically contain some form of lipid. Water itself can contribute to dryness and worsen the skin barrier, because prolonged contact with water can disrupt the stratum corneum and water rapidly evaporates after application.[5] Watery lotions can worsen the skin barrier and predispose to development of AD.[6] Therefore, ointments or thick creams rather than watery lotions are preferred in humans with AD.

Ingredients used in skin repair include combinations of petrolatum, vegetable oils, glycerin and urea.[7] Petrolatum has an immediate barrier-repairing effect[8] and is used in many over-the-counter products (e.g. Vaseline®, Hangzhou Jinque Home Product Co. Ltd, Xiaoshan, Hangzhou, China; Aquaphor®, Beiersdorf Inc., Wilton, CT, USA; and Cetaphil®, Galderma Laboratories L.P., Fort Worth, TX, USA). Paraffin oil and vegetable oils penetrate into the upper layers of the stratum corneum, and this is paralleled by a decrease in transepidermal water loss (TEWL), with the most effective occlusion seen with petrolatum.[9]

Large differences exist between products, and efficacy depends on the type of product and frequency of application. The choice and composition of the moisturizer are crucial in the long term. A study investigating the impact of long-term treatment with moisturizers on skin barrier function in healthy skin demonstrated that the effect is

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determined by the composition of the moisturizer.[10] Moisturizers have the ability to affect epidermal mRNA expression of genes for involucrin, transglutaminase 1 and kallikrein 5 and 7, either improving or worsening skin barrier function.[11]

Urea, a common moisturizing agent, is an endogenous metabolite that enhances stratum corneum hydration and has antimicrobial activity.[12] Topical application reduces dryness[13] and decreases TEWL.[14] Urea is not merely a passive metabolite, but a small-molecule regulator of epidermal structure and function by enhancing the expression of antimicrobial peptides, a property beneficial in patients with AD.[15]

In recent years, several no-steroidal barrier creams have been approved for AD treatment. EpiCeram® (PuraCap™; Pharmaceutical LCC, South Plainfield, NJ, USA) contains a combination of ceramides, cholesterol and fatty acids and was approved by the Federal Drug Administration (USA) in 2006.[16] Its efficacy was documented in a case series[17] and in a trial in patients with moderate-to-severe AD.[18] Remission of disease as established by the investigator under the global assessment was achieved by 58% of subjects after 3 weeks. Pruritus decreased markedly from baseline to week 3, regardless of severity at baseline. The efficacy of EpiCeram® was comparable to that observed with fluticasone propionate cream.[19] EpiCeram® reduced clinical disease severity and pruritus and improved sleep habits after both 14 and 28 days of therapy. Although the fluticasone group showed greater improvement at 14 days, improvement with EpiCeram® did not differ significantly from fluticasone by 28 days.

Atopiclair® (Galderma S.A., Lausanne, Switzerland) contains a combination of plant extracts, including glycyrrhetinic acid and *Vitis vinifera*. Atopiclair® is effective in the treatment of AD and has antipruritic properties in patients with mild-to-moderate AD.[20] Glycyrrhetinic acid, abundant in liquorice, can inhibit pruritus elicited by protease-activated receptor-2 agonists.[21] Humans with AD have higher levels of protease-activated receptor-2,[22] and this leads to increased permeability, barrier dysfunction, itching and inflammation.[23] Besides being antipruritic, glycyrrhetinic acid has antibacterial and antifungal properties that are beneficial in patients with AD.[24]

A recent study stirred debate because it showed a lack of significant difference in the clinical efficacy between a glycyrrhetinic acid-containing barrier repair cream (Atopiclair®), a ceramide-dominant barrier repair cream (EpiCeram®) and an over-the-counter petroleum-based skin protectant moisturizer (Aquaphor Healing Ointment®) applied three times daily for 3 weeks in children with mild-to-moderate AD.[25] These results clearly demonstrated that there are multiple valid approaches to skin repair.

Topical glucocorticoids and calcineurin inhibitors

As inflammation worsens the skin barrier, it is reasonable to propose that control of inflammation improves skin barrier function. Indeed, both topical calcineurin inhibitors and topical glucocorticoids (e.g. betamethasone) improve TEWL.[26] While both treatments decreased TEWL, electron microscopy of the skin after 3 weeks showed that only pimecrolimus-treated patients had an ordered stratum corneum with regular lamellar body extrusion, while the betamethasone-treated skin had inconsistent extracellular by-layers and only partly filled lamellar bodies. These results are consistent with the cutaneous atrophy observed clinically with betamethasone use, indicating that pimecrolimus is more appropriate for long-term therapy in terms of preservation of skin barrier. Pimecrolimus can also beneficially modulate expression of several genes involved directly in the skin barrier.[27] Tacrolimus, on the contrary, was reported to have negative effects on the skin barrier, including permeability and antimicrobial functions.[28] These effects were mediated by decreasing epidermal lipid synthesis, lamellar body secretion and expression of antimicrobial peptides.

What is known in dogs

Skin barrier dysfunction exists in AD[29,30] and may increase the risk of allergic sensitization.[31] Decreased ceramides[32,33] and abnormal stratum corneum ultrastructure have been described.[34,35] An increase in free and protein-bound glycosylceramides suggests an abnormality in metabolism of ceramides.[36] A significant decrease and altered metabolism of sphingosine-1-phosphate are described in lesional atopic skin compared with healthy skin.[37] All these studies emphasize the relevance of exploring skin barrier repair in veterinary medicine.

In dogs, the skin barrier is often assessed by TEWL, although the reliability of this methodology is not good.[38] A relationship between deficiency of ceramides and an increase in TEWL has been described,[39] while a relationship between disease severity and skin barrier dysfunction measured by TEWL has yet to be proved in dogs.[40] Thus, while it is reasonable to speculate that restoration of lipid deficiency should improve skin barrier function, it is still largely unknown whether skin barrier repair would directly translate into an improvement of clinical signs.

Lipid/ceramide-rich products

Topical application of ceramides, free fatty acids and cholesterol (Allerderm spot-on®; Virbac Animal Health, Fort Worth, TX, USA) improves the ultrastructure of the stratum corneum and increases the number of lipid lamellae.[41] Three weeks of topical application led to an increase in ceramide content and decrease in glucosylceramides. Normalization of protein-bound lipid content was also observed.[42] While these two studies showed a positive effect on lipid composition, demonstration of clinical benefit is still limited. An open study in dogs with chronic AD showed clinical improvement with twice-weekly application for 12 weeks, with a significant improvement of erythema noticeable after 6 weeks.[43] Although these results are promising, the impact of this study is limited by the small number of patients and the lack of a control group. A yet unpublished double-blinded, placebo-controlled study, applying the same emulsion three times weekly for 4 weeks, reported a significant decrease of clinical signs when compared with the control group, although the results on TEWL were mixed.[44] The lack of significant improvement in TEWL may be an indication of poor reliability of TEWL measurements rather than lack of skin barrier amelioration in light of the ultrastructural studies, although the ultrastructural studies

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did not evaluate the correlation between ultrastructure and TEWL measurements.[41]

An open study using a spot-on (once weekly) and a spray (once daily) containing essential oils and unsaturated fatty acids (Dermoscent Essential®; Laboratoire de Dermo-Cosmetique Animale, Castres, France) for 8 weeks[45] showed a significant decrease of clinical scores and pruritus in both groups, with no difference between groups. No improvement on TEWL was found. Oral administration of essential fatty acids [omega-6 (linoleic acid 350 mg/mL and γ-linolenic acid 45 mg/mL) and omega-3 (eicosapentaenoic acid 25 mg/mL and docosahexaenoic acid 28 mg/mL), mixed 5:1 (v/v); Megaderm®/EFA-Z® (Virbac S.A., Carros, France)] for 2 months also improved the ultrastructure and increased the lipid content in the skin of atopic dogs.[46] This feature was observed with both free and protein-bound lipids. No evaluation of the correlation with clinical improvement was reported.

Evidence to support the topical application of phytosphingosine is lacking at this time. A blinded, randomized controlled trial in atopic dogs using a phytosphingosine-containing shampoo (Douxocalm®; Sogeval Laboratories Inc., Irving, TX, USA) or a phytosphingosine-containing shampoo plus spray with similar ingredients or a control shampoo containing antiseptics, fatty acids and complex sugars (Allermyl®; Virbac Animal Health)[47] showed clinical improvement in all groups. No significant difference was found between groups. As all the interventions were theoretically able to affect the skin barrier, it is unknown whether using phytosphingosine provides extra benefit compared with any emollient or simple bathing. No assessment of skin barrier function was done in this study.

Barrier creams and other strategies

'Barrier cream' or skin protectants provide an exogenous barrier to water loss.[48,49] Dimethicone is an over-the-counter skin protectant.[50] Although this could be an effective and inexpensive strategy, a recent double-blinded, placebo-controlled study using dimethicone for 4 weeks in dogs with AD failed to demonstrate an improvement in clinical signs and TEWL.[51]

Ultrapure soft water, which is water in which calcium and magnesium ions have been replaced by sodium ions, has beneficial effects on the skin barrier compared with tap water.[52] In a randomized, controlled, cross-over study, shampoo treatment with ultrapure soft water significantly decreased pruritus and dermatitis scores, whereas shampoo treatment with tap water did not.[52]

Glucocorticoids, calcineurin inhibitors and allergen-specific immunotherapy

A preliminary study evaluating anti-inflammatory doses of oral prednisolone versus ciclosporin in dogs with AD failed to report a significant effect of time or group for TEWL after 4 weeks.[53] Clinical signs improved in both groups, but TEWL was not correlated with clinical improvement. On the contrary, successful allergen-specific immunotherapy was correlated with decreased TEWL when compared with atopic dogs that did not respond to allergen-specific immunotherapy.[54]

Concluding remarks

Skin barrier repair is a promising yet still incompletely explored approach to the management of canine AD. This approach could prove to be very beneficial when initiated early on in life and could possibly alter the course and minimize development of allergic sensitization. However, this approach needs to be evaluated carefully, because the choice of the wrong ingredients could have negative long-term effects and ultimately worsen an already impaired skin barrier. Thus, large controlled studies are still needed to identify the best treatment and the long-term effects on skin barrier function.

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Résumé
Des anomalies de barrière cutanée existent dans la dermatite atopique humaine et canine, menant à une augmentation de la perte hydrique et facilitant potentiellement la pénétration des allergènes et la sensibilisation. A la fois, les anomalies des lipides (e.g. les céramides) et des protéines (e.g.la filaggrine) ont été décrites. Certaines sont génétiques (e.g. les mutations de la filaggrine sont un des facteurs de risque principaux chez l'homme) et certains sont secondaires et liés à l'inflammation.

Chez l'homme, de nombreuses études ont montré l'efficacité des émollients et hydratants dans la restauration de barrière et cette approche a été pendant des années un pilier de la thérapie. Récemment, cette stratégie s'est avérée prometteuse en prévention.

En médecine vétérinaire, les preuves concernant les défauts de barrière cutanée se développent rapidement. Une diminution des céramides et de la filaggrine (chez certaines catégories de chiens) ont été décrites. Un métabolisme modifié des céramides a également été proposé. Malgré ces données préliminaires et la disponibilité des produits commercialisés afin d'améliorer la barrière cutanée, les preuves d'efficacité clinique de réparation cutanée est encore limitée. Des études préliminaires ont démontré que l'application topique d'acides gras et de céramides ainsi que l'administration systémique d'acides gras améliorent les défauts de lipides dans la peau de chiens atteints de dermatite atopique mais peu de preuves cliniques existent.

La rémission de la maladie chez l'homme est accompagnée par une amélioration de la barrière cutanée à la fois par les inhibiteurs de la calcineurine et par les glucocorticoïdes. En médecine vétérinaire, une étude préliminaire sur la cyclosporine et la prednisone n'a pas permis de détecter une amélioration significative de la perte hydrique alors qu'une immunothérapie efficace corrélait avec une amélioration de la barrière cutanée. De larges études contrôlées sont nécessaires pour savoir quelle approche de réparation cutanée serait la plus efficace et si cela peut être utilisé comme une stratégie préventive.

Resumen
Tanto en la dermatitis atópica humana como canina se observa una alteración de la función de barrera de la piel, lo cual lleva a una perdida elevada de agua y potencialmente favorece la penetración y la sensibilización a alergenos. Se han descrito tanto anormalidades en los lípidos (por ejemplo ceramidas) como en las proteínas (por ejemplo filagrina). Algunos defectos son hereditarios (por ejemplo las mutaciones en la molécula de filagrina son uno de los factores de riesgo principales en seres humanos) y algunas son secundarias y ligadas a inflamación.

En seres humanos numerosos estudios han demostrado la eficacia de emolientes y de cremas hidratantes en la restauración de la barrera, y este acercamiento ha sido durante años la base principal de la terapia. Recientemente, esta estrategia terapéutica también ha demostrado ser prometedora como función preventiva.

En veterinaria, existen cada vez mas evidencias respecto a la alteración de la función de barrera de la piel. Se han descrito disminuciones en las ceramidas y la filagrina (en algunos grupos de perros). También se ha propuesto un metabolismo alterado de las ceramidas. A pesar de estos datos preliminares y de la disponibilidad de productos para mejorar la función de barrera de la piel, las pruebas con respecto al beneficio a nivel clínico de la mejora esa función de barrera son todavía limitadas. Estudios preliminares han demostrado que el uso tópico de ácidos grasos y de ceramidas y la administración sistémica de ácidos grasos mejoran las deficiencias en los lípidos en la piel de perros con dermatitis atópica, pero existen mínimas evidencias clínicas.

La remisión de la enfermedad en seres humanos es paralela a una mejora de la función de barrera de la piel, en personas tratadas tanto con inhibidores de calcineurina como con glucocorticoides. En veterinaria, un estudio preliminar utilizando ciclosporina y prednisona no pudo detectar una mejora significativa de la pérdida de agua, mientras que la inmunoterapia se correlacionó con una función de barrera mejorada. Se necesitan estudios controlados con mayor numero de animales para abordar la cuestión de cual es la mejor estrategia para mejorar la alteración de la barrera de la piel y si esta estrategia podría utilizarse como terapia preventiva.

Zusammenfassung
Eine Dysfunktion der Hautbarriere besteht sowohl beim Menschen als auch bei Hunden mit atopischer Dermatitis, was zu erhöhtem Wasserverlust führt und möglicherweise das Eindringen der Allergene und in der Folge eine Sensibilisierung ermöglicht. Es wurden Abweichungen sowohl bei den Lipiden (z.B. bei den Ceramiden) als auch bei Proteinen (z.B. bei Filaggrin) beschrieben. Einige sind genetisch bedingt (z.B. sind Filaggrinmutationen unter den wichtigsten Risikofaktoren beim Menschen), einige treten sekundär auf und stehen im Zusammenhang mit einer Entzündung.

Beim Menschen haben zahlreiche Studien die Wirksamkeit von Weichmachern und Feuchtigkeitsspendern bei der Wiederherstellung der Barriere beschrieben und diese Ansicht spielte seit Jahren eine zentrale Rolle bei der Therapie. Unlängst konnte auch gezeigt werden, dass diese Strategie auch eine präventative Wirkung hat.

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In der Veterinärmedizin steigt die Evidenz im Bezug auf eine Beeinträchtigung der Hautbarriere drastisch an. Verminderte Konzentrationen an Ceramiden und Filaggrin (in einigen Untergruppen von Hunden) sind beschrieben. Die Hypothese eines veränderten Metabolismus der Ceramide wurde auch aufgestellt. Trotz dieser vorläufigen Daten und der Verfügbarkeit von Produkten, die die Verbesserung der Hautbarriere bewerben, ist die Evidenz, dass Interventionen im Bereich der Hautreparatur einen klinischen Nutzen bringen, noch immer limitiert. Vorläuferstudien haben gezeigt, dass die topische Applikation von essentiellen Fettsäuren und Ceramiden, sowie die systemische Administration von essentiellen Fettsäuren die Lipiddefizite in der Haut von Hunden mit atopischer Dermatitis, verbessern; klinische Evidenz liegt allerdings nur begrenzt vor.

Die Remission der Erkrankung ist beim Menschen von einer verbesserten Hautbarriere begleitet, die sowohl durch Calcineurin Inhibitoren wie auch durch Glukokortikoide erreicht wird. In der Veterinärmedizin konnte eine Vorläuferstudie mit Ciclosporin und Prednisolon keine signifikanten Verbesserungen des Wasserverlusts zeigen, während eine erfolgreiche Immuntherapie mit einer verbesserten Hautbarriere einherging. Kontrollierte, große Studien sind notwendig, um abzuklären in welcher Form eine Reparatur der Haut klinisch am effektivsten ist und ob dieses Vorgehen präventativ eingesetzt werden kann.

要約

皮膚バリア機能不全はヒトとイヌアトピー性皮膚炎の両方で存在し、水分喪失量が増加し、アレルゲンを侵入させ感作を助長させる可能性がある。脂質（例、セラミド）や蛋白質（例、フィラグリン）の両方の異常が報告されてきた。ある部分は遺伝性で（例、フィラグリン変異はヒトで主要なリスク因子）、ある部分は二次的で炎症に関与している。

ヒトでは、多くの研究で皮膚軟化剤や保湿剤がバリアの修復に効果のあることが示されており、この治療法は長い間治療の中心となってきた。近年では、この方法は予防的な機能があることが期待されている。

獣医療では、皮膚バリア障害に関する研究は急速に増えている。セラミドとフィラグリン（一部の犬の集団にて）が減少していると報告されている。セラミドの代謝活性の変化も示されている。それらの予備データや市販の皮膚バリアを改善する製品が利用できるにもかかわらず、皮膚のバリア機能を修復する治療法の臨床的な有効性の報告は限られている。予備的な研究により，犬のアトピー性皮膚炎に脂肪酸やセラミドの外用塗布あるいは脂肪酸の全身投与すると皮膚の脂質欠乏は改善することが示されたが、臨床的な報告は限られている。

ヒトの疾患での寛解はカルシニューリン阻害剤やグルココルチコイド投与による皮膚バリアの改善と並行している。獣医療では、シクロスポリンとプレドニゾロンによる予備研究では水分喪失の有意な改善を示さなかったが、有効であった免疫療法は皮膚バリアの改善と相関していた。どの皮膚バリアの修復方法が臨床的に最も効果的であるか、その方法は予防的にも用いることができるかという問題に取り組むには大規模な比較研究が必要であろう。

摘要

人类和犬的异位性皮炎都存在皮肤屏障功能紊乱，导致水分流失增加和促进潜在过敏原的侵入和致敏。脂质（如神经酰胺） 和蛋白质（如丝聚蛋白）均有异常。 有些是基因遗传 （例如人的丝聚蛋白突变是主要原因），而有些是继发性并与炎症有关。

人的很多研究表明润肤剂和保湿剂有助于恢复屏障功能，这种方案多年来一直被做为支柱性治疗。近来，这个功能作为预防策略有望成功。

在兽医学中，皮肤屏障损伤的证据正在迅速建立，发现了神经酰胺和丝聚蛋白（一些犬的亚型）的减少，还提出了神经酰胺代谢的改变。尽管有这些改善皮肤屏障初始数据，市场上也有相关产品存在，但是关于促进皮肤修复的临床好处的证据很有限。初步研究证明局部使用脂肪酸和神经酰胺，并全身使用脂肪酸改善异位性皮炎犬的皮肤脂质缺乏，但临床证据有限。

在人医中，疾病的缓解与改善皮肤屏障，同时使用钙神经素抑制剂和糖皮质激素并行。在兽医上，初步研究发现环孢素和泼尼松不能显著改善水份流失，然而成功的免疫疗法与皮肤屏障的改善相关。对照之下，需要大量研究去寻找在临床中最有效的皮肤修复方法，且这种方法是否可作为预防策略使用。

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