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Molecular Mechanisms of Skin Barrier Dysfunction and Targeted Repair Strategies: Evidence Evaluation from Basic Mechanisms to Clinical Translation

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Abstract: ***The skin barrier is composed of stratum corneum keratinocytes and their surrounding lipid matrix, epidermal cell junctions, keratinization differentiation programs, protease regulation, and the skin surface microenvironment. Barrier abnormalities can increase transepidermal water loss and enhance skin susceptibility to irritants, allergens, and microbial-related factors; inflammation, in turn, can affect keratinocyte differentiation and lipid metabolism. This article reviews the molecular basis of barrier homeostasis focusing on filaggrin (FLG), tight junctions, stratum corneum lipids, lamellar bodies and lipid transport, skin pH, and protease regulation, and discusses intervention directions including basic moisturization, inflammation control, nuclear receptor signaling, and the microbiome. This article distinguishes between measures supported by human clinical research and guidelines, evidence from cellular/animal mechanisms, and research hypotheses yet to be verified. Existing evidence supports gentle care and regular moisturization as the basis for barrier management; if inflammatory diseases such as atopic dermatitis are present, evidence-based anti-inflammatory treatment should be adopted according to disease severity. The biological plausibility of a single molecular pathway cannot be directly equated with clinical efficacy.***

Keywords: Skin barrier, Stratum corneum, Filaggrin, Ceramide, Tight junction, Protease, Atopic dermatitis**.**

1. Introduction and Structural Basis of the Barrier

From a research design perspective, the barrier is not a single "switch" but multiple interdependent functional layers. The structural integrity of the stratum corneum, the degree of order of the lipid layer, the maturation state of keratinocytes, and the connections of the living epidermis collectively determine barrier performance. Environmental or inflammatory factors may first affect one of these links, and then expand to other links through feedback effects. Therefore, studies should clearly specify whether the discussion focuses on water retention, exogenous substance permeability, keratinization maturation, or inflammation control, to avoid referring to different outcomes collectively as "barrier repair". Individual differences also affect research results, including age, anatomical site, climate, washing and care habits, and previous skin diseases, all of which influence baseline measurements [1].

The skin barrier is an important interface between the body and the external environment. Its functions not only include reducing water loss, but also restricting the entry of irritants and some exogenous substances, and participating in local immune and microecological homeostasis [2]. Barrier function is often evaluated by indicators such as transepidermal water loss (TEWL), stratum corneum water content, skin surface pH, and clinical symptoms. Different indicators reflect different aspects of the barrier, and a single indicator cannot fully represent the health status of the barrier [3]. "Barrier impairment" is not a single disease. Dry environments, frequent cleaning, irritating chemicals, occupational exposure, aging, hereditary keratinization abnormalities, and inflammatory skin diseases can all cause barrier changes, and their dominant mechanisms and treatment priorities are not the same [4]. Atopic dermatitis (AD) is an important disease for studying the interaction between barrier and inflammation, but not all findings in AD can be directly extrapolated to normal dry skin, contact dermatitis, or hereditary keratinopathies [5-9].

This article adopts a narrative review approach, integrating traceable reviews, mechanistic studies, and clinical guidelines, focusing on explaining why key molecules are important, the level of evidence, and how mechanistic findings can be carefully translated into nursing or treatment strategies. This article is not a systematic review or meta-analysis: no pre-registered search protocol, double screening, or formal risk of bias assessment was conducted, so no quantitative grade judgment is made on all evidence.

The stratum corneum is often summarized as "bricks" composed of keratinocytes and "mortar" composed of intercellular lipids. Keratinocytes are not inert fillers, but the end products of the keratinization differentiation program; intercellular lipids are not a uniform oil film, but a highly ordered lamellar structure formed by ceramides, cholesterol, and free fatty acids [5,6]. TEWL can be used to estimate the transepidermal loss of water, stratum corneum water content reflects the hydration state of the surface layer, and skin surface pH is related to lipid processing and protease activity. Research reports should specify environmental conditions and measurement methods, and combine patient-related outcomes such as clinical severity, pruritus, recurrence, and quality of life as much as possible.

2. Key Molecules: FLG, Cornified Envelope, and Tight Junctions

FLG-related studies suggest that genetic susceptibility and acquired factors should be discussed separately. Carrying loss-of-function variants increases the risk of some diseases, but the penetrance is not 100%; the absence of known variants does not rule out abnormal barrier function. For reduced FLG expression, inflammatory environments and changes in keratinocyte differentiation may be involved, so not all low expression can be explained by genetic causes. Rigorous papers should distinguish between different levels: genotype, protein expression, natural moisturizing factor levels, and clinical phenotype.

Tight junction studies also have problems with sampling and causal direction. Decreased expression of a certain connexin in lesional skin may be involved in permeability changes, or it may be a secondary change caused by inflammation. The types of evidence provided by histology, cell models, and human clinical observations are different, and correlations should be avoided being written as definite causality [10]. Filaggrin (FLG) is processed from a precursor protein expressed by keratinocytes, and is involved in aggregating keratin intermediate filaments and affecting keratinocyte morphology and stratum corneum structure. Amino acids and their derivatives produced by FLG degradation are important components of natural moisturizing factors. Loss-of-function variants of FLG are associated with increased risk of ichthyosis vulgaris and AD, but not all AD patients carry FLG variants [7,8].

Therefore, FLG is an important mechanistic node, but not a "master switch" that can alone explain all barrier abnormalities. Treatment concepts targeting FLG include improving keratinization differentiation, regulating its expression, or compensating for hydration function; however, local moisturization cannot be described as repairing the genetic variant itself, and the restoration of a certain marker in experimental models does not mean that it has been proven to prevent recurrence or change the long-term disease course. Structural proteins such as loricrin (LOR), involucrin (IVL), and other structural proteins participate in the formation of the cornified envelope and keratinocyte maturation, and their differentiation stages and functions are not completely the same as those of FLG.

Tight junctions are composed of claudin family, occludin, and ZO and other scaffold proteins, and participate in the regulation of intercellular paracellular permeability in the granular layer. Systematic reviews have summarized studies on the association between tight junction abnormalities and AD, but there are differences in tissue sampling, disease course, site, and detection techniques among studies [11]. Tight junctions and the stratum corneum lipid barrier are at different levels: the former mainly regulates the permeability between living epidermal cells, while the latter is the key structure of the stratum corneum that restricts the passage of water and substances. Barrier defects and inflammation have a bidirectional effect: barrier abnormalities may promote the entry of exogenous substances and activate epithelial immune responses; inflammatory factors, in turn, can alter keratinocyte differentiation, lipid synthesis, and barrier protein expression [10].

3. Lipid Matrix, Lamellar Bodies, and pH/Proteases

A common misconception in lipid research is equating total lipid content with barrier quality. Actual barrier function is jointly related to lipid categories, molecular chain length, saturation, ceramide subclasses, and the arrangement of the lamellar structure. Even if the total amount is similar, differences in composition or arrangement may alter permeability [12]. Interpretation of evidence for topical lipid products also requires caution: different formulations may contain different ceramides, cholesterol, fatty acids, and carrier systems, and the test results of one product cannot be generalized to all similar products [13]. The transport and processing of lipid precursors involve multiple steps, and genetic defects in lipid transport molecules can lead to severe keratinization disorders [14].

The main categories of intercellular lipids in the stratum corneum are ceramides (CERs), cholesterol, and free fatty acids. Their relative proportions, ceramide subclasses, fatty acid chain length distribution, and lipid arrangement can all affect barrier permeability. Studies have shown that changes in lipid composition and tissue arrangement can be observed in inflammatory skin diseases; however, specific changes vary by disease type, lesional and non-lesional skin, age, and analytical methods [1,5,6]. This means that "containing ceramides" is not a sufficient evaluation criterion for formulations. The lipid type, concentration, ratio, carrier, stability, and actual usage of topical preparations may all affect the results.

Lamellar bodies are important organelles for keratinocytes to transport lipids and processing enzymes to the stratum corneum. Lipid precursors undergo secretion, enzymatic transformation, and ordered arrangement to form the intercellular lamellar lipid matrix. This process requires coordination of ceramide, cholesterol, and fatty acid metabolism; increasing a single type of lipid alone does not necessarily restore all processing steps [6,14]. Genetic defects in lipid transport-related molecules such as ABCA12 can cause severe keratinization diseases, indicating that lipid transport is crucial for barrier formation. Specific commensal Staphylococcus epidermidis can promote the production of protective ceramides through a sphingomyelinase-related process, a finding that further reveals the potential role of microbe-lipid interactions in barrier homeostasis [15].

There is a spatially varying acid-base environment on the skin surface and within the stratum corneum, which is involved in lipid processing, stratum corneum desquamation, and protease regulation. A 2024 study using in vivo pH imaging further described pH changes in different regions during stratum corneum differentiation, suggesting that the simplified description of "the entire stratum corneum has only a fixed pH value" is insufficient [16]. Stratum corneum desquamation relies on proteases to degrade intercellular connections at the right location and time. Serine proteases such as KLK5 and KLK7 are regulated by endogenous inhibitors and the microenvironment, and their physiological and pathological roles have been detailed in multiple reviews

[17]. Deficiency of LEKTI encoded by the SPINK5 gene can lead to protease imbalance, abnormal stratum corneum connections, and obvious barrier damage in Netherton syndrome [17,18].

4. Intervention Strategies: Basic Care, Anti-Inflammation, and Molecular Pathways

The selection of care measures should also take sustainability into account. Excessive cleaning, frequent product changes, or simultaneous application of multiple active ingredients may increase irritation and make the source of adverse reactions difficult to determine. In practical management, simplifying the routine, introducing products gradually, observing tolerance, and recording symptom changes are usually more conducive to identifying effective regimens than pursuing complex ingredients. Evidence-based treatment does not mean that everyone adopts the same regimen; guideline recommendations need to be combined with indications, disease severity, age, site, comorbidities, and patient preferences for shared decision-making.

Moisturizers can improve dryness by reducing water evaporation, absorbing moisture, softening the stratum corneum, or supplementing some lipids. Basic care usually includes gentle cleansing, reducing hot water and excessive washing, avoiding known irritants, timely moisturizing after bathing, and adjusting product texture according to season and site. Moisturizers are not a homogeneous category: occlusives, humectants, and emollients have different main mechanisms of action. The 2023 American Academy of Dermatology guidelines for the topical treatment of adult AD provide evidence-based recommendations for moisturizers, topical corticosteroids, calcineurin inhibitors, and some PDE-4/JAK inhibitors [19]. Ordinary dryness can be managed with basic care first; if persistent erythema, obvious pruritus, exudation, pain, signs of infection, or recurrent attacks occur, the cause should be evaluated by medical professionals [20].

Moisturizing can relieve dryness and support barrier management, but in active AD, moisturizing alone is usually insufficient to control inflammation. Standard treatment requires the selection of anti-inflammatory drugs according to disease severity. The effects, indications, and risks of topical corticosteroids, calcineurin inhibitors, and specific new topical drugs are different, and prescription drugs should not be used for a long time on your own under the pretext of “repairing the barrier” [19]. Nuclear receptors can affect keratinocyte differentiation, lipid synthesis, processing, and secretion, and related reviews discuss the roles of pathways such as PPAR, LXR, VDR, RAR/RXR, AHR, PXR, and FXR in the epidermal lipid barrier [21]. These pathways constitute potential drug development directions, but the mechanistic plausibility of targets needs further verification through randomized controlled trials.

Tapinarof is a topical aryl hydrocarbon receptor (AHR) agonist that has shown efficacy in randomized clinical trials for plaque psoriasis [22]. This result proves that specific AHR modulators can have clinical value in specific indications, but the immune mechanisms and treatment goals of psoriasis and AD are not the same, and it cannot be inferred that all AHR agonists can repair the barrier. The scope of application of any drug should be subject to regulatory approval information and disease guidelines.

5. Microbiome, Research Limitations, and Future Directions

Microbiome research requires particular attention to differences at the strain level. Different strains of the same species may have different metabolic capabilities and host interactions, and the species name alone is insufficient to predict effects. Detection of changes in the abundance of a certain microorganism by sequencing does not mean that the microorganism plays a causal role in the disease; diet, drugs, care products, skin site, and disease severity may all affect the microecology. Future intervention studies should clarify strain identity, active ingredients, administration methods, stability, and safety monitoring, and use appropriate controls.

Another limitation of literature reviews is publication bias: positive or novel results are more likely to be published, while negative studies may be less accessible. Different papers may also use different disease definitions, detection platforms, and endpoints, resulting in heterogeneity of results. Therefore, reviews should avoid selecting only studies that support preset views, and clearly state uncertainties when evidence is insufficient. Skin microorganisms are not universally harmful, and their effects depend on species, strain, skin site, host immune status, and ecological environment. A 2022 mechanistic study reported that specific commensal Staphylococcus epidermidis can promote the production of protective ceramides through a sphingomyelinase-related process and help reduce skin dehydration in experimental models [23]. This is an important mechanistic finding, but it does not mean that standardized probiotic or microbiome products are already available to safely and effectively treat human barrier diseases.

Barrier repair studies should clearly distinguish between surrogate endpoints and patient-important outcomes. A decrease in TEWL or an increase in stratum corneum water content may indicate biophysical improvement, but it does not necessarily mean a synchronous improvement in pruritus, recurrence, or quality of life. Studies should also consider natural disease fluctuations, season, baseline severity, adherence, concomitant medications, and vehicle effects. If a trial only observes short-term outcomes, includes only a small sample, or lacks appropriate controls, strong causal conclusions should not be drawn.

This article summarizes the evidence into three levels: the first level includes clinical measures supported by clinical guidelines, randomized controlled trials, or systematic reviews; the second level includes human observational studies and tissue/molecular studies related to diseases; the third level includes cellular, animal, or early experimental studies, which are suitable for proposing hypotheses rather than directly guiding clinical practice. Future studies should improve phenotypic precision, stratifying by AD, irritant contact dermatitis, hereditary keratinization abnormalities, etc.; unify measurement methods; fully report topical lipid formulations and preparation characteristics; and establish a verifiable evidence chain between human tissues, clinical

trials, and real-world data.

6. Conclusion

The core conclusion of this article is that molecular mechanisms can help explain barrier abnormalities, but clinical decision-making should still be based on specific disease diagnosis and evidence quality. FLG, lipid metabolism, tight junctions, pH, and protease regulation are not isolated targets independent of each other, but jointly participate in the homeostatic network. For mechanistic studies, their models and limitations should be clarified; for clinical studies, priority should be given to reproducible symptom improvement, reduced recurrence, and safety, rather than just changes in individual biomarkers.

The skin barrier relies on the synergy of stratum corneum structural proteins, intercellular lipids, living epidermal cell junctions, lamellar body secretion, protease regulation, and the skin microenvironment. FLG, ceramides, tight junctions, the KLK-LEKTI axis, and nuclear receptor pathways provide important clues for explaining barrier homeostasis, but the evidence levels and clinical operability of each target are different. At this stage, gentle cleansing, regular moisturization, and avoidance of irritation are the basis for barrier management; for patients with inflammatory skin diseases, evidence-based anti-inflammatory treatment should be combined after professional evaluation. For the microbiome, microplastics, and new molecular targets, scientific interest should be maintained, while avoiding exaggerating early mechanistic findings as definite therapeutic effects.

The core task in the future is not to continue stacking candidate molecules, but to verify whether these molecular changes can bring perceptible benefits to patients, and clarify the applicable population, effect size, durability, safety, and cost. Only by connecting mechanistic evidence with standardized clinical research can barrier repair move from conceptual publicity to reproducible and evaluable clinical practice.

7. Supplementary Discussion on Evidence Evaluation and Clinical Translation

The strength of evidence for barrier repair research needs to be judged in combination with the study design, not solely based on whether the conclusion is positive. Well-designed randomized controlled trials can estimate intervention effects, but are still affected by factors such as sample size and follow-up duration; observational studies are suitable for describing associations but are difficult to eliminate confounding; cellular or animal models are mainly used to explain mechanisms and propose hypotheses. Different types of evidence have their own value and cannot replace each other. The improvement of barrier indicators by a pathway in a model does not mean that related topical products are effective for patients.

Endpoint selection also affects study interpretation. Changes in biophysical indicators such as transepidermal water loss and stratum corneum water content may not correspond one-to-one with symptoms perceived by patients such as pruritus, dryness, and recurrence. Ideal clinical studies should report both objective measurements and patient-important outcomes, specifying the minimal clinical difference, statistical uncertainty, and adverse events. A 2024 review of ceramide formulations emphasized that products labeled as “containing ceramides” cannot be assumed to have equivalent repair capabilities [24].

Clinical translation requires clarifying the applicable boundaries of conclusions. For example, “an intervention is effective in trials of adult plaque psoriasis” does not mean “the pathway can repair all skin barriers”. This article adopts a clinical evidence-oriented approach to intervention strategies: basic care and moisturization are the basis for barrier management; inflammatory skin diseases require anti-inflammatory treatment according to guidelines; new strategies need to be judged based on indications and evidence maturity. Future trials should pre-register protocols, report complete formulations and procedures, use appropriate controls and sufficient follow-up, and disclose negative results.

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