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REVIEW

Beyond the Skin: Exploring the Gut-Skin Axis and Metabolic Pathways in Atopic Dermatitis Pathogenesis

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Video Abstract

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Abstract: Atopic dermatitis (AD), is a chronic, recurrent inflammatory skin condition characterized by eczema-like lesions, itching, and dryness. It often coexists with other atopic comorbidities, including food allergies (FA), allergic rhinitis (AR), and allergic asthma (AA). The pathogenesis of AD is complex and multifactorial, involving immune dysregulation, epidermal barrier disruption, and dysbiosis of intestinal and skin microbiota. Recent research has increasingly focused on the gut-skin axis, highlighting the role of intestinal microbiota and their metabolic products in regulating skin immunity and barrier function. Dietary changes and metabolic pathway modulation are emerging as promising therapeutic strategies. This article reviews recent advancements in AD research across three dimensions: gut microbiota, metabolomics, and comorbidities, while exploring potential therapeutic approaches to regulate gut microbiota and target metabolic pathways.

Keywords: dermatitis, atopy, gut microbiota, metabolomics, comorbidity

Introduction

Atopic dermatitis (AD) is a widespread chronic inflammatory skin disorder marked by eczema-like lesions, intense itching, and dryness. These symptoms can vary significantly among individuals and often occur alongside multi-system inflammatory conditions. Epidemiological studies indicate an alarming rise in AD incidence globally, with prevalence rates reaching 15%–30% among children, many of whom continue to experience symptoms into adulthood, contributing to an adult prevalence rate of approximately 10%.[1,2] In China, around 20% of the population is affected by AD and other allergic diseases, which significantly diminish patients' quality of life and impose a considerable socioeconomic burden.[3,4] In addition to its progression patterns, AD frequently coexists with other atopic conditions, such as food allergies (FA), allergic rhinitis (AR), and allergic asthma (AA). This article consolidates recent research findings regarding AD and its associated comorbidities, emphasizing gut microbiota, metabolomics, and underlying mechanisms to provide insights for future investigations.

Pathogenesis of Atopic Dermatitis

The pathogenesis of AD is driven by five key factors: altered immune responses, genetic predisposition, epidermal barrier dysfunction, dysbiosis of skin and gut microbiota, and environmental stimuli (Figure 1).[4] Immunologically, type 2 inflammation is predominantly mediated by Th2 cells, ILC2s, and their associated cytokines.[5] Besides stimulating B-cell proliferation and antibody production, type 2 inflammatory cytokines (IL-4, IL-5, IL-9, and IL-13) have also been associated with humoral immunity, barrier immunity in mucosal surfaces, and modulation of anti-parasitic infections and allergic/atopic.[6] This indicates that type 2 inflammation is central to the entire process of AD pathogenesis.[1] Depending on various factors such as disease stage, duration, patient age, and ethnicity, Th2-driven immune responses may activate

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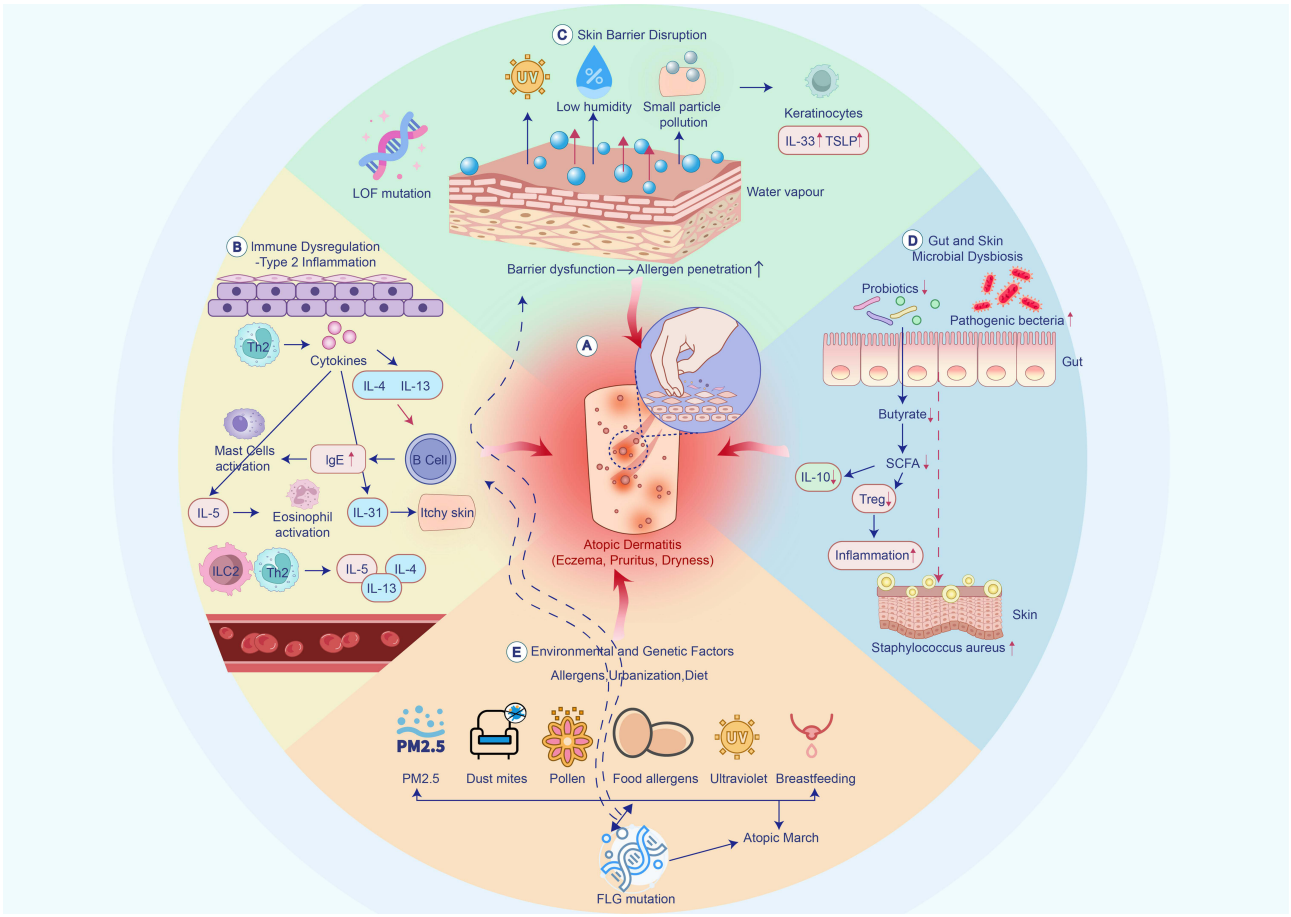

Figure 1 The multifactorial pathogenesis of atopic dermatitis. At the center is skin inflammation (**A**), surrounded by five key pathogenic factors: immune dysregulation (**B**), epidermal barrier disruption (**C**), gut and skin microbial dysbiosis (**D**), genetic susceptibility and environmental triggers (**E**). The diagram first highlights immune dysregulation dominated by Th2 cells. IL-4 and IL-13 promote B cell–mediated IgE production, leading to mast cell activation; IL-5 recruits eosinophils; IL-31 contributes to itch transmission; and ILC2 cells further amplify the inflammatory response by secreting the same cytokines (**B**). The mechanism of barrier disruption is shown through LOF mutations in the FLG gene and damage to the stratum corneum caused by environmental exposures. These changes lead to upregulation of epithelial cytokines such as IL-33 and TSLP, increased transepidermal water loss, and enhanced allergen penetration, exacerbating local inflammation (**C**). Dysbiosis of the skin and gut microbiota plays a bidirectional role in AD. Overgrowth of Staphylococcus aureus is both a consequence and a driver of skin barrier dysfunction and inflammation. In parallel, gut microbiota imbalance may trigger systemic immune activation and further worsen skin inflammation (**D**). Genetic and environmental factors act synergistically. FLG mutations are closely linked to earlier onset and persistent AD, while environmental factors can suppress FLG expression, further compromising the skin barrier. Together, they may contribute to the progression of the "atopic march" (**E**).

Abbreviations: Th, T-helper cell; IL, interleukin; ILC, innate lymphoid cell; LOF, loss-of-function; FLG, filaggrin; TSLP, thymic stromal lymphopoietin; SCFA, Short-Chain Fatty Acids; Treg, regulatory T cell.

Th1, Th17, and Th22 cytokine pathways (Figure 1B).[4] Genetically, loss-of-function (LOF) mutations in the filaggrin (FLG) gene are significant contributors to AD development, with environmental factors also influencing FLG expression.[7] Low humidity and ultraviolet (UV) radiation can downregulate FLG, compromising the skin barrier and increasing vulnerability to allergens.[7] Patients with LOF mutations often experience more severe disease phenotypes, including earlier onset and persistent symptoms.[7] Furthermore, FLG mutations have been linked to a significantly elevated risk of childhood AD and may indirectly lead to other allergic comorbidities in AD patients.[8] This phenomenon highlights the significance of promptly identifying AD phenotypes and biomarkers.[9] It is also noteworthy that itching, FLG mutations, and environmental exposure could simultaneously trigger skin barrier disruption in AD patients, allowing oxygen to penetrate the skin, thus leading to anaerobic microbiota reduction and creating new ecological niches for bacterial growth (Figure 1C and E).[10] These ecological niches or changes in skin pH, among other factors, could also induce microbiota dysbiosis in AD patients.[10] Furthermore, they could promote *staphylococcus aureus*.[10] 10 Additionally, intestinal inflammation and dysbiosis—characterized by an altered firmicutes/bacteroidetes ratio—have been associated with systemic immune activation and exacerbation of skin inflammation.[11] Exposure to various

environmental factors, including allergens, pollution, infections, and harsh detergents, as well as breastfeeding duration, may also heighten the risk of AD (Figure 1D and E).[4] Despite substantial research advancements regarding these factors, the underlying mechanisms remain partially understood.

Historically, research on AD has predominantly focused on local immune dysregulation and skin barrier defects. However, emerging evidence suggests that AD is a systemic condition. Its association with multiple gastrointestinal, allergic, and psychiatric comorbidities indicates a shared pathophysiological basis between the skin and distant organs, such as the gut.[12,13] In this context, the gut microbiota—central to regulating systemic immune and inflammatory responses—has become a focal point in AD research for its role in modulating skin immune homeostasis and barrier function through the gut-skin axis.[14] Understanding microbial composition alone is insufficient; the critical challenge lies in deciphering microbial metabolites, which is the focus of metabolomics. These metabolites can enter systemic circulation and influence skin immune cell differentiation and inflammatory pathways.[15] Therefore, integrating gut microbiome and metabolomic analyses is essential for unravelling the mechanisms underlying AD identifying novel biomarkers, and developing targeted interventions.

Atopic Dermatitis and the Gut Microbiota

The gut, being the largest digestive organ in the human body, performs essential functions, including digestion and absorption of food, metabolic regulation, and information transmission. The gut microbiota comprises all microorganisms residing in the gastrointestinal tract (GIT), including bacteria, archaea, fungi, and some protozoa and algae, along with their genetic material and metabolic products.[16] The intestinal environment itself (including molecules secreted by both the human body and microorganisms) has been established to contribute to this complex system.[16] In children aged 2–3 years, the gut microbiota is already largely developed and continues to maintain a mutually beneficial symbiotic relationship with the intestinal microenvironment during host development.[17] At the phylum level, beneficial bacterial communities in the gut of healthy adults include Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia, with Firmicutes and Bacteroidetes accounting for up to 90% of the microbial community. At the genus level, *Prevotella and Bacteroides* are the most abundant genera in the gut microbiota.[18] Functionally, the gut microbiota plays a crucial role in maintaining intestinal epithelial integrity, facilitating digestion, metabolism and synthesizing beneficial substances, including vitamins. Metabolites and signaling molecules produced by gut microbiota, such as peptides involved in ribosomal synthesis, amino acid metabolites, short-chain fatty acids (SCFAs), oligosaccharides and non-ribosomal peptides contribute to the formation of a mucus layer in the gut, regulating systemic immune responses and significantly influencing the pathogenesis of allergic and skin illnesses.[19,20]

Gut Microbiota Dysbiosis in Atopic Dermatitis

Gut microbiota dysbiosis refers to pathological changes in microbial community composition and function, leading to reduced diversity and imbalances among specific microbial groups. It is often observed in AD patients, especially during childhood, manifesting as reduced probiotic levels, increased abundance of pathogenic bacteria, and decreased microbial diversity.[21–23] Impaired maturation of the microbiota by age one is commonly associated with childhood allergic diseases, including AD. Numerous cohort studies have indicated a reduction in probiotic such as *Anaerostipes hadrus, Fusicatenibacter saccharivorans, Eubacterium hallii*, and *Blautia wexlerae* in affected children, while pathogenic bacteria like *Eggerthella lenta, Escherichia* coli, *Enterococcus faecalis, Clostridium innocuum*,and *Tyzzerella nexilis* showed increased abundance.[22,23] Furthermore, elevated levels of *Streptococcus* coupled with decreased levels of *Clostridium* and *Akkermansia* may suggest persistent and worsening AD, whereas higher levels of *Akkermansia* could indicate AD remission.[24] In adult AD patients, characteristic dysbiosis features include reduced abundance of *Prevotella* and *Bacteroides* and increased presence of *Enterococcus* and *Staphylococcus aureus*.[25] Mouse model studies have demonstrated that pretreatment with *azithromycin* led to an increase in four gut bacterial genera *(Bacteroides, Candidatus_Saccharibacteria_unclassified, Acetatifactor, and Firmicutes_unclassified)* while decreasing three gut bacterial genera *(Alistipes, Clostridiales_unclassified,and Butyricicoccus)*. These findings suggest that azithromycin pretreatment may worsen AD severity in mouse models due to alterations in gut microbiota balance.[26]

Gut-Skin Axis

Changes in gut microbiota composition can significantly impact immune system function and metabolite production, indirectly influencing skin health by regulating immune responses and barrier integrity. Besides originating from the same embryonic layer, skin and intestinal cells have similar signal transductions and neural innervation pathways.[27] This phenomenon highlights the "gut-skin axis"—a concept of a functional link between the gut and skin, a potentially significant avenue for understanding how microbial metabolites influence skin and immune cells.[14] Dysbiosis in gut microbiota may impair immune function in AD patients, leading to chronic inflammation and exacerbation of skin symptoms.[13] It can also compromise the integrity of the intestinal epithelium, reduce epidermal hydration, and weaken skin barrier function, ultimately increasing intestinal permeability. Consequently, toxins, undigested food particles, and gut microorganisms may infiltrate the systemic circulation. Upon reaching target tissues, including the skin, these components could upregulate pro-inflammatory cytokines IL-6 and IL-17, thus inducing a robust Th2 immune response, which, in turn, might exacerbate the skin's immune reaction and compromise stratum corneum function, ultimately contributing to AD pathogenesis and progression.[11,26] Additionally, Toll-like receptor 2 (TLR2) responses correlated positively with the relative abundance of *Prevotella* in the gut microbiota and negatively with the relative abundance of *Bacteroides*.[18] Moreover, intestinal flora dysbiosis-induced chronic inflammatory response may disrupt the gut microbial structure, thereby decreasing the number of beneficial microorganisms and the proliferation of pathogenic microorganisms, thus sustaining and exacerbating the inflammatory condition and creating a vicious cycle.[28]

Applications of Probiotic Therapy

As previously discussed, the interaction between the gut microbiota and the intestinal immune system can be targeted to treat or prevent diseases by enhancing local immune function and reshaping the intestinal microenvironment through modulation of the microbiota composition.[29] Probiotic supplementation was reported to exert multifaceted effects on the gut microbiome, including the capacity to inhibit pathogens competitively, modulate microbial composition and metabolism, and restore immune balance.

Interventional studies have demonstrated that probiotic supplementation can alleviate symptoms of AD by reducing allergic inflammation through the regulation of T-cell responses and immune factors. This provides direct evidence for the causal relationship between microbiota and immune system regulation.[30–32] Probiotic mixtures containing Bifidobacterium have been shown to effectively alleviate inflammation in AD mouse models by regulating gut microbiota and metabolites, thereby promoting anti-inflammatory and antioxidant states.[33,34] In addition, a multitude of case-control studies have corroborated the finding that probiotics, such as Lactobacillus plantarum, have the capacity to diminish the levels of eosinophils and IL-4 in the human body. Moreover, these probiotics can enhance the functionality of tight junctions in intestinal epithelial cells, thereby facilitating the competitive exclusion of pathogens. These effects have been demonstrated to enhance intestinal barrier function and elevate SCORing Atopic Dermatitis (SCORAD) scores in patients diagnosed with AD.[35–37]

Atopic Dermatitis and Metabolomics

Presently, AD is largely recognized as a complex systemic disease, especially with recent advances in multi-omics technologies. Metabolomics has elucidated the molecular mechanisms of AD from a novel perspective. Its research methods primarily rely on mass spectrometry (MS) and nuclear magnetic resonance spectroscopy (NMRS), which enable the systematic detection of metabolites in blood, urine, and tissue samples, thereby providing technical support for understanding disease-related metabolic network regulation.[38] Moreover, metabolites, which are often at the terminal end of an organism's metabolism, are closest to the observed phenotype. Owing to their distinct attributes, they could be examined to understand disease pathogenesis, facilitating early and differential diagnosis, as well as the monitoring of pharmacotherapeutic responses.

Analysis of the relationship between gut microbiota and metabolites requires effective differentiation between correlation and causation. The extant clinical studies have predominantly revealed statistical associations between the

two, while establishing causal mechanisms requires validation through interventional experiments. The ensuing discourse will delve into this subject in conjunction with the levels of evidence from pertinent research.

Gut Microbiota Dysbiosis in Atopic Dermatitis

Gut microbiota-produced metabolites and signalling molecules can regulate systemic immune function, maintain immune balance, resist infection and inflammation, and impact skin health.[19,21,39] Furthermore, gut microbiota-produced metabolites could influence homeostasis. The gut microbiome exerts its effects via metabolites such as SCFAs, amino acids, vitamins, and bile acid metabolites, of which SCFAs and tryptophan are the two most extensively studied metabolite categories—both having specific absorption pathways and receptors through which metabolites can perform systemic functions.[15]

Short-Chain Fatty Acids

Intestinal microorganisms, particularly the anaerobic bacterial phyla Bacteroidetes and Firmicutes, are capable of fermenting dietary fiber to produce SCFAs, including formic acid, acetic acid, propionic acid, butyric acid, valeric acid, hexanoic acid, isobutyric acid, and isovaleric acid.[40,41] These SCFAs are among the most extensively studied metabolic products of intestinal bacteria.[40,41] Acetate, propionate, and butyrate constitute the majority of SCFAs found in the human gut, often accounting for over 90% of all SCFAs.[40] Notably, SCFAs could interfere with immune responses at multiple levels, affecting intestinal and epithelial barrier function—a key contributor to AD occurrence, thus creating conditions favorable for allergen penetration and further sensitization.[41,42] In patients with AD, the imbalance in gut microbiota leads to abnormal SCFA metabolism, marked by decreased butyrate levels. This contributes to the development of AD by disrupting the intestinal barrier and promoting immune imbalance.[43] Research has demonstrated that butyrate demonstrates anti-inflammatory effects through its direct interaction with intestinal epithelial cells, macrophages, B cells, and plasma cells, while concurrently regulating the differentiation of effector T cells.[40]

Children with AD exhibited significant abnormalities in SCFA metabolism in the gut microbiota.[44] Furthermore, the pediatric AD group showed reduced butyrate levels in the gut microbiota, as well as a significant reduction in the abundance of butyrate-producing bacteria with age, indicating a significant negative correlation with serum IgE levels.[44] Moreover, the AD group exhibits downregulation of key genes involved in butyrate synthesis, such as GPR109A and PPAR-γ, with the most pronounced differences observed in older infants.[44] The researchers also conducted animal experiments, confirming that AD model mice exhibited a reduced expression of butyrate receptors and transcription factors (TFs) in colonic tissues, along with decreased fecal butyrate concentrations and elevated acetate levels, implying a metabolic shift from butyrate synthesis.[44] In vitro studies further demonstrate that physiological concentrations of butyrate significantly enhance oxygen consumption rates in intestinal epithelial cells, indicating that butyrate boosts mitochondrial oxidative phosphorylation and minimizes intestinal oxygen leakage, thereby preserving the anaerobic environment.[44] Collectively, these findings indicate that disruptions in the butyrate metabolic pathway in AD patients could disturb the homeostasis of microbiota-host interactions, exacerbating disease onset through immune regulation and redox imbalance. Moreover, butyrate may promote the formation of the IL-10 receptor, crucial for maintaining barrier function, and may regulate the expression of essential junctional proteins, thereby influencing interactions between the microbiota and the intestinal lumen, and potentially leading to epithelial barrier dysfunction.[45] Furthermore, disorders of butyrate metabolism not only affect the intestinal epithelium but also correlate with compromised skin barrier function, highlighting the interplay between gut health and skin integrity. Experimental studies in mouse models show that a high-fiber diet or oral administration of butyrate can enhance keratinocyte differentiation and the expression of barrier-related proteins, significantly improving skin barrier function. This finding provides substantial evidence in support of the causal mechanism of the gut-skin axis.[21] The researchers also discovered that butyrate salts could facilitate the metabolic reprogramming of mitochondrial fatty acid oxidation in keratinocytes, thereby strengthening skin barrier integrity.[21] This phenomenon increases the synthesis of keratinization envelope proteins, such as keratin and FLG, as well as barrier lipids, such as ester-linked-omega-hydroxy (EO) ceramides, ultimately reducing allergen penetration and inflammatory responses.[21] Additionally, the activation status of antigen-presenting cells (APCs) and T cells in the skin was significantly reduced, particularly with the inhibition of TH2-type immune responses, supporting the hypothesis that butyrate exerts a dual effect on the skin barrier. On the one hand, it could enhance skin barrier function, thereby reducing allergen

penetration. On the other hand, butyrate was shown to regulate immune cell activity, thus alleviating inflammatory responses.[21] Dietary interventions grounded in the principle of gut microbiota rebalancing, encompassing galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS), have been shown to enhance total fecal short-chain fatty acids, particularly acetate and butyrate. This, in turn, has been observed to alleviate symptoms associated with AD and even counteract symptoms of depression that are commonly associated with AD.[46,47] This finding suggests a potentially efficacious therapeutic approach.

Significant changes in acetate and propionate levels have been noted in the gut microbiota of children with AD.[40,48] Research by Wang et al identified a negative correlation between acetate levels in breast milk from mothers of exclusively breastfed infants and the presence of AD in children.[48] They also implemented a combined intervention using 2'-FL and *Bifidobacterium*, which enhanced acetate and propionate production in the gut microbiota of infants with AD, simultaneously remodelling gut structure.[49] Notably, transplantation of this remodeled microbiota into AD mice significantly alleviated symptoms. Further analysis using RNA sequencing and non-targeted metabolomics via liquid chromatography-mass spectrometry (LC-MS) revealed activation of the retinol metabolic pathway in murine subjects post-intervention, alongside significantly elevated plasma retinoic acid levels and a negative correlation with AD biomarkers.[49] Additionally, LI D et al demonstrated that propionic acid could inhibit inflammatory responses in the intestines and skin of AD mice through the G protein-coupled receptor 43/NF-κB pathway, thereby improving skin AD symptoms.[50] In vitro studies also indicate that propionate alleviates skin itching and reduces the density of intraepidermal nerve fibers. Reduced responsiveness of dorsal root ganglion neurons to itch stimuli has been shown to mitigate excessive excitability in sensory neurons. Additionally, propionate inhibits the release of neurogenic mediators, such as calcitonin gene-related peptide, thereby further reducing pruritus and cutaneous inflammation. These findings suggest that regulating skin itching through the metabolic activities of gut microbiota, particularly involving SCFAs, may represent a novel therapeutic avenue for the treatment of AD.[51]

Tryptophan

Tryptophan, an essential aromatic amino acid, plays pivotal roles in intestinal immune regulation, protein synthesis, and the production of bioactive molecules. These molecules could be metabolized via three distinct pathways to produce indole and indole-derived metabolites, including indole lactate (ILA), indole-3-carbinol (I3C), and indole-3-propionic acid (IPA).[52,53] Indole derivatives could act as ligands for the aryl hydrocarbon receptor (AhR)—a ligand-activated TFs expressed by various cells in the skin, which has been crucially implicated in skin integrity and immunity maintenance. A deficiency in the tryptophan metabolic pathway has been previously observed in individuals with AD.[54]

At the molecular level, AhR activation is crucial for maintaining intestinal epithelial barrier function by enhancing tight junction protein expression, promoting mucus secretion, and facilitating goblet cell differentiation.[55,56] Consequently, a decrease in tryptophan metabolites can undermine the intestinal barrier, allowing pro-inflammatory substances such as lipopolysaccharide (LPS) to enter the bloodstream. This infiltration has been linked to the onset of systemic low-grade inflammation and the facilitation of Th2-type immune responses.[57] This systemic immune dysregulation affects the skin through the "gut-skin axis", where inadequate AhR activation fails to inhibit IL-4/IL-13-mediated STAT6 signalling pathways. As a result, there is a reduction in the expression of essential barrier proteins, such as filaggrin, leading to compromised skin barrier function.[58] This paper aims to present compelling evidence from animal studies that supports this hypothesis. For instance, research by Fang et al using a mouse model demonstrated that oral administration of the AhR ligand I3C decreased disease activity, evidenced by reduced skin thickness, IgE levels, and concentrations of Th2-associated cytokines (TSLP, IL-4, IL-5).[59] Furthermore, supplementation with probiotics, such as *Limosilactobacillus reuteri*, was shown to elevate serum tryptophan metabolite levels, thereby alleviating inflammation and reducing itching behaviour.[60] Thirion et al demonstrated a positive correlation between clinical severity of AD and a pro-inflammatory tilt in gut microbiota tryptophan metabolism, while downregulation of this pathway via interventions (eg, balneotherapy) coincided with marked skin inflammation remission, providing crucial clinically relevant evidence.[61] This finding suggests that a novel therapeutic strategy for AD may be represented by targeting the gut microbiota-tryptophan-AhR axis. However, AhR activation exhibits high context dependency, and excessive activation may paradoxically induce inflammation or pruritus.[62] A separate human study indicated that the clinical improvements in skin

observed with the targeted drug dupilumab, a monoclonal antibody that blocks IL-4 and IL-13, occur through modulation of the indole pathway of tryptophan metabolism, influencing gut bacterial function.[63] This effect may be attributed to the drug's ability to suppress Th2 immune responses, resulting in broad anti-inflammatory actions that manifest systemically, including in the skin and gastrointestinal tract. Despite these insights, the biological processes involved in tryptophan metabolism are intricate.[64] Currently, the clinical application of tryptophan and its derivatives lacks validation, and the long-term efficacy and safety of their therapeutic potential remain uncertain.[64]

Atopic Dermatitis Blood Metabolites

Zeng Y et al, through LC-MS analysis, detected characteristic metabolic imbalances, featuring significantly upregulated pro-inflammatory metabolites (eg, styrene) and generally downregulated protective metabolites (eg, betaine and taurine), in the serum of AD patients.[65] They also conducted pathway analysis, which indicated that activation of the mTOR signaling pathway and alterations in glycerophospholipid metabolism could exacerbate inflammatory responses and disrupt the skin barrier, worsening disease progression. Conversely, the taurine metabolism and betaine synthesis pathways, which possess antioxidant and immunomodulatory functions, were significantly suppressed.[65] Additionally, Ma EZ et al performed a cohort study and detected branched-chain amino acids (BCAAs, eg, isoleucine, valine, and leucine), aromatic amino acids (AAAs, eg, tyrosine, tryptophan, and phenylalanine), carnitine, and indole-3-acetic acid (IAA) in the plasma of AD patients.[66] The observed reduction in BCAAs was linked to metabolic reprogramming during inflammatory conditions, potentially fostering Th2 differentiation via the mTOR pathway—aligning with the regulatory functions of IL-4/IL-13 on lipid metabolism. Furthermore, positive correlations among carnitine, tryptophan, and Th2 cytokines TARC and MCP-4 imply that metabolic dysfunction may aggravate Th2 inflammation.[66]

Wang Y et al conducted a comprehensive cross-organ metabolomics analysis, confirming the presence of synergistic metabolic disorders in the skin and circulatory system of AD patients. They identified five common differentially expressed metabolites, including prostaglandin D2 (PGD2), platelet-activating factor (PAF), and Glutamine, in a mouse model.[67] The aforementioned perspective is currently devoid of corresponding clinical research evidence to support it. Among these, PGD_2 could promote inflammation via the cheiloid receptor homologous molecule expressed on Th2 cells (CRTH2), while PAF, a potent lipid inflammatory mediator, could activate platelets and neutrophils. The levels of glutamine, an amino acid, were also found to be elevated in the skin but downregulated in serum, reflecting a high demand for keratinocyte proliferation.[67] The researchers also reported concurrent changes in histidine metabolism, pyrimidine metabolism, and the glutamate pathway, emphasizing their significance in AD pathogenesis.[67] Another thorough analysis revealed a substantial reduction in the levels of five distinct lysophosphatidylcholine (lysoPC) isomers in the serum of pediatric AD patients. The researchers also found a negative correlation between lysoPC levels and SCORAD scores, mite-specific IgE, and eosinophil percentages, implying the exacerbation of inflammatory responses—a phenomenon attributable to the weakened anti-inflammatory function of lysoPC.[68] They also Furthermore, the synchronous reduction in both unsaturated and saturated lysoPC levels underscores the complexity of metabolic regulation in AD. Further validation through animal models is essential to establish a causal relationship.[68]

A Dupilumab intervention study revealed that patients exhibited significantly reduced serum phosphatidylcholine (PC) levels post-treatment. This effect was achieved via phospholipase A2 (PLA2) inhibition to reduce arachidonic acid (AA) release, thus decreasing pro-inflammatory mediator production.[69] This drug primarily regulates glycerophospholipid metabolism and the AA metabolic network, ultimately lowering the levels of pro-inflammatory factors such as IL-6, IL-10, and IFN-γ, which confirms its efficacy through metabolic-immune interactions.[69]

It is important to note that current metabolomics research may be limited by small sample sizes, uncontrolled dietary confounding factors, and a lack of validation for the causal relationships between the microbiota and metabolites. Therefore, integrating multi-omics technologies with functional experiments is crucial for a more comprehensive understanding of the molecular mechanisms underlying key metabolic pathways in AD pathogenesis, as well as for enhancing the potential for clinical application.

Metabolic Products of the Skin Microbiota in Atopic Dermatitis

The skin microbiome is crucially involved in the immune response and metabolic regulation of AD. Previous targeted metabolomics analysis of metabolic products in the skin of AD patients and normal control groups revealed significant inter-group differences in 77 metabolic products, including amino acids, biogenic amines, acylcarnitines, sphingomyelin, and phosphatidylcholine.[70] Most research on AD skin metabolites focuses on lipids, with a particular emphasis on direct skin monitoring of metabolites.[10] Dessì A et al recently examined the changes in the lipidome of the stratum corneum across different body regions (eg, forehead, elbow crease, and forearm) in AD patients and healthy subjects. Compared to healthy skin, AD skin exhibited marked differences in lipid small molecules. Notably, although the total lipid content in the stratum corneum of AD patients was generally elevated, their lipid profile was abnormal, characterized by a decrease in long-chain ceramides and an increase in short-chain ceramides—changes especially pronounced in sebaceous gland-rich areas like the forehead.[71] Relative to healthy skin, AD patients lost the physiological gradient where long-chain ceramides were more concentrated in the forehead compared to the elbow crease and forearm.[71] The researchers also found that *Staphylococcus aureus* colonization was significantly positively correlated with specific ceramide subtypes and negatively correlated with palmitic acid.[71] Moreover, these alterations were independent of the FLG gene mutation status, suggesting that mechanisms beyond those associated with classical barrier genes may regulate the abnormalities in small molecules within the skin in AD.

Skin microbiome dysbiosis may influence metabolic pathways, including purine, pyrimidine, and histidine metabolism, thereby exacerbating inflammatory responses and disrupting the skin barrier. This connection underscores its positive correlation with the clinical severity of AD.[67,72] A previous cross-sectional study revealed that affected skin regions in AD patients showed a significant upregulation of xanthine, which was positively correlated with the abundance of *Staphylococcus* and the clinical severity of AD, as assessed using the Eczema Area and Severity Index (EASI) score.[72] The significant upregulation of xanthine in AD lesions suggests purine metabolism pathway activation. Due to inflammation or barrier damage-induced heightened cellular DNA repair demands in AD skin, hypoxanthine, a critical intermediate in nucleic acid metabolism, may accumulate, potentially promoting inflammatory responses.[72] In an AD mouse model, LC-MS DEM analysis of diseased skin yielded 220 significantly altered metabolites, of which uracil, lysoPC, and PGD_2 were significantly upregulated, whereas uric acid (UA) and inosine were significantly downregulated.[67] Uracil upregulation within the pyrimidine metabolic pathway may facilitate *Staphylococcus aureus* proliferation, thus intensifying infection and inflammation. Concurrently, elevated skin 1-Methyhistamine, N-Acetylhistamine levels and decreased UA levels were observed in the histidine metabolic pathway. Since UA serves as an ultraviolet (UV)-protective agent, its reduction could aggravate skin barrier damage. The researchers also integrated microbiome and metabolome analyses to clarify the relationship between skin microbiota dysbiosis and metabolic disturbances in AD patients, alongside the potential molecular mechanisms.[67]

To briefly outline key metabolic alterations in AD, we have summarized major findings in Table 1, highlighting the direction of changes, underlying mechanisms, and potential implications for the pathogenesis of AD.

Atopic Dermatitis and Comorbidities

Atopic dermatitis is frequently associated with a range of comorbidities, including dermatological, allergic, metabolic, respiratory, gastrointestinal (GI), cardiovascular, autoimmune, musculoskeletal, ophthalmological, oncological, and psychiatric disorders, with particular emphasis on allergic comorbidities in recent studies.[73–77] The term "allergic comorbidity" refers to the coexistence of at least one additional allergic condition in AD patients. Notable allergic comorbidities include AR, FA, allergic conjunctivitis, and AA. According to epidemiological reports, 40.5% and 25.7% of individuals with AD also experience AR and FA, respectively, with the co-prevalence rate of both conditions standing at 14.2%. Furthermore, AD patients exhibited a 2.16-fold higher risk of developing AA compared to the general population.[78] The prevalence rates of FA in adult AD patients were also established to be 28.6% and 24.1%, respectively.[78,79] Moreover, these numbers were reported to be as high as 30–40% among children with AD.[80] Notably, these allergic conditions often manifest in a sequential developmental pattern, starting with AD and FAs in infancy, followed by AA and AR onset during childhood, a progression commonly known as the atopic or allergic

Table 1 Summary of Key Metabolite Alterations in AD

Metabolite Class	Key Changes in AD	Examples	Mechanisms and Impacts
SCFAs	Reduced butyrate and propionate; altered acetate levels	↓ Butyrate, Propionate ↑ Acetate	Impairs intestinal barrier integrity; promotes systemic inflammation; reduces skin barrier function; dysregulates immune response[21,41,45]
Tryptophan metabolites	Decreased indole derivatives (I3C, IPA)	↓ I3C, IPA ↓AhR activation	Compromised gut and skin barriers; enhanced Th2 immune response; reduced anti-inflammatory capacity[55,59,60]
Amino acids	Altered BCAAs and AAAs	↓ Isoleucine, Valine, Leucine ↑ Tyrosine, Phenylalanine	Promotes Th2 differentiation via mTOR pathway; correlates with Th2 cytokine levels; indicates metabolic reprogramming[67]
Lipids and Fatty acids	Reduced lysoPC; altered ceramide profiles	↓ LysoPC isomers ↓ Long-chain ceramides ↑ Short-chain ceramides	Weakens anti-inflammatory function; disrupts skin barrier; correlates with disease severity and IgE levels[69,72]
Inflammatory mediators	Elevated prostaglandins and platelet-activating factor	↑ PGD2 ↑ PAF	Promotes inflammation via CRTH2 receptor; activates platelets and neutrophils; exacerbates immune response[68]
Neuro-immune metabolites	Altered histamine and uric acid levels	↑ 1-Methylhistamine, N-Acetylhistamine ↓UA	Enhances pruritus and inflammation; reduces UV protection; aggravates skin barrier damage[68,73]
Bile acids and others	Altered bile acid metabolism; retinoic acid pathway activation	↑ Retinoic acid Altered bile acid profiles	Modulates immune response; enhances barrier function; negatively correlates with AD biomarkers[50,70]

Notes: ↑ indicates increase; ↓ indicates decrease.

Abbreviations: AD, atopic dermatitis; SCFAs, short-chain fatty acids; AhR, aryl hydrocarbon receptor; I3C, indole-3-carboinol; IPA, indole-propionate; BCAAs, branched-chain amino acids; AAAs, aromatic amino acids; lysoPC, lysophosphatidylcholine; PGD2, prostaglandin D2; PAF, platelet-activating factor; UA, uric acid; UV, ultraviolet.

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march.[3,81] This sequence illustrates the transition from cutaneous and GI inflammation to respiratory tract inflammation. Overall, the severity of AD is correlated with an increased risk of atopic comorbidities.[78]

Common Immune Mechanisms of Atopic Dermatitis Comorbidity

Besides influencing the entire AD pathogenesis, type 2 inflammation-driven immune dysregulation also serves as a common pathogenic mechanism for allergic comorbidities such as AA and AR.[12] According to reports, environmental and genetic factors could disrupt the epidermal barrier, induce immune dysfunction, and upregulate type 2 inflammatory cytokines, including IL-4, IL-5, and IL-13. This cascade often triggers inflammatory responses that result in type 2 inflammatory diseases affecting the skin, respiratory tract, and digestive tract.[82] In AD patients, IL-4 and IL-13 can compromise skin barrier integrity, facilitating allergen penetration and contributing to the development of other type 2 inflammatory conditions.[83–85] Disorders such as AD, AA, chronic prurigo, chronic urticaria, and chronic sinusitis with nasal polyps (NPs) exemplify type 2 immune response disorders.[85] Additionally, epithelial cell (EC)-derived cytokines, such as IL-25, IL-33, and TSLP, not only drive type 2 immune responses but also crucially modulate the pathogenesis of AD and AA.[82,86] Moreover, elevated levels of type 2 cytokines, such as IL-4 and IL-13, are detectable in the skin lesions of AD patients, while IL-31 was closely linked to AD-associated pruritus.[83]

Gut Microbiota and Their Metabolites in Atopic Dermatitis Comorbidity

Individuals with comorbid AD often exhibit significant dysbiosis and metabolic irregularities, alongside disrupted metabolic pathways. A bidirectional two-sample Mendelian randomization analysis has established a causal relationship between specific gut microbiota and conditions such as AD, AR, and AA. Furthermore, the genera *Dialister* and *Prevotella*—major SCFA producers—could inhibit Th2/Th17 inflammatory responses and promote regulatory T cell (Treg) differentiation, conferring a protective effect in the intestines of AD patients. In AR patients, the class *Coriobacteriia* and its taxonomic subunits, including the order *Rhamnobacter*, exhibit protective effects, while the family *Victivallaceae* is associated with an increased risk of disease. Additionally, an elevated abundance of the genus *Holdemanella* has been noted in AA patients, potentially modulating SCFA levels and promoting Th2-type inflammatory responses.[87]

Disruption of early gut microbiota and metabolic dysfunction can persist into adulthood, potentially influencing the onset and progression of allergic comorbidities. Research has shown that the relative abundance of the family *Ruminococcaceae* is often elevated in fecal samples from infants who develop allergic diseases between 2 and 12 months, which correlates with the onset of allergic diseases.[88] Furthermore, *Bifidobacteria* can induce the production of Foxp3+ Treg cells and suppress inflammatory responses. Colonization with *Bifidobacterium* during the neonatal period may lower the risk of developing AA later in life, while an early microbial imbalance, such as non-*Bifidobacterium* dominance, may elevate the risk of allergic diseases.[89] It is noteworthy that allergic children often display a persistent abundance of genera such as *Bacteroides, Prevotella*, and *Ruminococcus*, which may be linked to impaired immune regulatory functions.[90,91] Additionally, reduced abundance of *Faecalibacterium* has been associated with a higher risk of AA, whereas increased levels of *Escherichia coli* could promote AA onset.[92] Multi-omics analyses have further demonstrated that significantly reduced abundance of *R. gnavus* in early-onset persistent phenotypes corresponds with lower intestinal acetate levels, potentially linked to ACSS2 and JAK-STAT signalling pathways, along with systemic Th2 inflammatory responses.[93]

The gut microbiota produce various metabolic products—among which SCFAs serve as key mediators and are the most abundant—through which they exert a significant influence on allergic disease onset and progression.[94] According to research, infants aged over one year and with elevated butyrate and propionate levels in their fecal samples are often at a significantly lower risk of developing allergies later in life.[95] Conversely, those with diminished acetate levels during pregnancy or early infancy were associated with an increased risk of AA.[95]

The onset and progression of AD comorbidities are intricately linked to gut microbiota dysbiosis, abnormal metabolite production (such as SCFAs and tryptophan derivatives), and an immune regulation imbalance. Therefore, early gut microbiota modulation and immune system intervention, along with other measures that modify disease progression, may reduce the risk of these comorbidities.

Conclusion

Atopic Dermatitis is a systemic condition characterized by immune, metabolic, and microbiome dysregulation, often accompanied by allergic processes and multisystem comorbidities. It is crucial for therapeutic approaches to transition from merely managing symptoms to prioritizing disease modification. This shift necessitates early intervention within the gut-skin axis, along with the modulation of microbiota and immune-metabolic pathways, leading to substantial changes in disease progression. Clinically, there is a pressing need to improve patient education and management strategies to enhance treatment adherence and quality of life. An integrative approach that combines the holistic perspective of Traditional Chinese Medicine with the foundational theories of modern Immune-Mediated Inflammatory Diseases (IMID) and Immune-Mediated Skin Diseases (IMSD). The integration of the commonalities in chronicity, systemic involvement, and inflammatory pathways between AD and other immune-inflammatory disorders provides new insights for a comprehensive understanding of AD. Future efforts should focus on developing disease-modifying therapies, including small-molecule drugs and JAK inhibitors. Exploring cross-disease treatment strategies based on shared mechanisms of IMID and IMSD holds great promise for creating effective, long-lasting solutions for AD patients.

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Disclosure

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