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REVIEW

A Conceptual Review of Gut, Skin, and Oral Microbiota in Autoimmune Bullous Diseases: From Dysbiosis to Therapeutic Potential

Hanxiao Xu, Sizhe Li, Sihan Liu, Ya-Gang Zuo

Department of Dermatology, National Clinical Research Center for Dermatologic and Immunologic Diseases, Translational Medicine Center, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China

Correspondence: Ya-Gang Zuo, Department of Dermatology, National Clinical Research Center for Dermatologic and Immunologic Diseases, Translational Medicine Center, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100730, People's Republic of China, Email zuoyagang@263.net

Abstract: Autoimmune bullous diseases (AIBDs), including pemphigus and bullous pemphigoid, are chronic inflammatory skin disorders characterized by dysregulated immune responses mediated by autoantibodies that target adhesion molecules in the skin and mucous membranes. Emerging evidence highlights the pivotal role of host microbiota dysbiosis in AIBDs pathogenesis, offering novel insights into disease mechanisms and therapeutic strategies. This review systematically synthesizes the current findings on gut, skin, and oral microbiota alterations in AIBDs, emphasizing their contributions via the gut-skin axis, microbial metabolites, and pathogen-host interactions. Key innovations include uncovering how specific pathogenic and commensal microbiota influence disease progression through intriguing skin inflammation and direct barrier impairment. Notably, while some microbiota changes overlap with other dermatoses, AIBDs exhibit distinct microbial signatures associated with their unique autoimmune mechanisms targeting adhesion molecules. Furthermore, we explore microbiota-targeted therapies, such as antibiotics, probiotics, and fecal microbiota transplantation, and demonstrate their potential to restore microbial homeostasis and improve clinical outcomes. By integrating multi-omics evidence and clinical data, this review bridges mechanistic insights with translational applications, proposing microbiota modulation as a promising adjunctive therapy for AIBDs. Our analysis identifies critical research gaps, including the need for longitudinal studies and personalized microbial interventions, positioning this review at the forefront of microbiome-inflammation-autoimmunity research.

Keywords: autoimmune bullous diseases, microbiota dysbiosis, skin inflammation, gut-skin axis, microbial metabolites, microbiota-targeted therapies

Introduction

Bullous diseases represent a group of dermatological diseases characterized by blisters and erosions in the skin and/or mucous membranes.[1] According to their pathogenesis, these disorders are divided into autoimmune bullous diseases (AIBDs) and non-autoimmune bullous diseases, with AIBDs being more prevalent. Pemphigus vulgaris (PV) and bullous pemphigoid (BP) are two major types of AIBDs, distinguished by their blister localization patterns: PV presents with intra-epidermal acantholysis, while BP exhibits sub-epidermal detachment.[1,2]

The pathogenesis of AIBDs is predominantly attributed to IgG autoantibodies targeting adhesion structures (desmosomes and hemidesmosomes) in the skin and mucous membranes.[2] In pemphigus, the loss of cell-cell adhesion (desmosomes) between keratinocytes leads to acantholysis and intra-epidermal blister formation. Desmogleins (Dsg), the core structural proteins of desmosomes, are targeted by pathogenic IgG autoantibodies, with two predominant types implicated: pemphigus vulgaris antigen (Dsg3) and pemphigus foliaceus antigen (Dsg1).[2] Eight distinct types of pemphigus have been identified: PV, classical pemphigus foliaceus (PF), endemic pemphigus foliaceus (fogo selvagem), pemphigus vegetans, pemphigus herpetiformis, IgA pemphigus, paraneoplastic pemphigus, and drug-induced

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pemphigus.[3] Among these, PV and PF represent their predominant forms globally.[3] Existing research has mainly focused on PV, while other pemphigus types lack valuable research due to their low incidence.

In pemphigoid, the disruption of cell-basement membrane adhesion (hemidesmosomes) results in subepidermal blister formation. The main subtypes include BP, mucous membrane pemphigoid (MMP), and epidermolysis bullosa acquisita.[3] As the most common type, BP is mediated by IgG autoantibodies targeting the bullous pemphigoid antigen (BPAg) in hemidesmosomes, specialized structures anchoring the epidermis to the basement membrane zone.[2] Two types of BPAg are recognized: BPAg1 (BP230), localized to the inner dense plaque of the hemidesmosome, and BPAg2 (BP180), a transmembrane glycoprotein of the hemidesmosome.[1]

Additionally, numerous studies have revealed that imbalanced T cell subsets [T helper (Th) cells and regulatory T (Treg) cells] and associated cytokines are critical players in the pathogenesis of AIBDs, especially the decreased Th1/Th2 ratio and increased Th17/Treg balance.[4]

The human microbiota comprises numerous microorganisms, including bacteria, fungi, and viruses, which colonize various body sites, particularly the gastrointestinal tract, skin, and oral cavity. These microorganisms significantly affect host physiology, such as metabolism, immune modulation, barrier function, pathogen colonization, drug reaction, and even brain functions.[5] In turn, various host factors, such as age, diet, immunity, and regional pH, can shape the microbial community.[6] Briefly, there are complicated interactions between human health conditions and the microbiota community. 16S rRNA gene sequencing (16Ss) is widely used to characterize the composition of human microbiota due to its high resolution and practical applicability.[7] The development of sequencing platforms remarkably improved the understanding of the role that microbial communities play in human health and disease.[8] Metagenomic shotgun sequencing provides superior species-level resolution and functional profiling over 16S sequencing.[9]

The diversity of microbiota is typically assessed using two key indicators: alpha diversity (within-sample diversity) and beta diversity (between-sample similarity).[10] For alpha diversity, the Shannon and Chao1 indices serve as key tools to respectively reflect microbial taxon evenness and richness, while the Bray-Curtis dissimilarity index is preferred for beta diversity assessment.[11] This systematic review synthesizes current evidence on microbiota alterations in AIBDs, offering novel insights into the pathogenesis and potential therapeutic approaches from a microbiota perspective.

Alterations of Host Microbiota in Patients with AIBDs

Pemphigus

Gut Microbiota

The gut-skin axis has been shown to be involved in various skin diseases, with the gut microbiota (GM) playing a vital role through multiple mechanisms.[12] GM consists of trillions of microorganisms colonizing the gastrointestinal tract, predominantly bacteria. The major phyla include Firmicutes (60–70%), Bacteroidetes (20–30%), Actinobacteria (1–10%), and Proteobacteria (<5%).[13]

At the 16s rRNA level, studies have not identified a significant difference in GM diversity (both alpha and beta) between PV patients and healthy controls (HCs).[14–16] However, a greater beta diversity has been observed in PV patients using metagenomic sequencing technology[17,18] which can identify differential bacteria at the species level.[9,19,20]

At the phylum level, PV patients are characterized by a significant decrease in Firmicutes and an increase in Proteobacteria.[17] Moreover, the reduction in Firmicutes appears to correlate with disease severity, while its restoration following treatment parallels clinical improvement.[18] Firmicutes-derived short-chain fatty acids (SCFAs), particularly butyrate, exert anti-inflammatory effects in multiple ways, while also strengthening the intestinal barrier and reducing pathogen permeability.[21,22]

Specific butyrate-producing bacteria, such as *Faecalibacterium prausnitzii* and *Roseburia intestinalis*, are reduced in GM.[17] Consistently, the levels of GM-derived SCFAs decrease in PV.[18] The reduction of butyrate-producing flora has been linked to the overexpression of pro-inflammatory cells and auto-inflammation in Crohn's disease,[23] suggesting a similar mechanism may operate in PV. A significant enrichment of Proteobacteria in the gut of PV patients has been confirmed by several studies.[14,16–18] At the species level, opportunistic pathogens such as *Escherichia coli, Klebsiella pneumoniae*, and *Enterobacter hormaechei* are significantly increased.[17,18] These gram-negative bacteria produce

lipopolysaccharide (LPS), a major virulence factor that induces a regional inflammatory response and impairs the intestinal barrier. This impairment allows toxins, antigens, and bacteria to pass through, potentially leading to the onset and progression of autoimmune disease. In addition, a positive correlation among these species implies a potential reciprocal relationship between the harmful bacteria.[17]

The trend of the Bacteroidetes phylum is different in several studies, and species from Bacteroidetes exhibit divergent tendencies.[14,17,18] Probiotics such as *Bacteroides ovatus* and *Bacteroides uniformis* (SCFAs producers) decrease in pemphigus patients,[18] while pathogenic bacteria such as *Bacteroides fragilis* increase.[17]

Cutaneous Microbiota

The skin, a vital interface with the external environment, harbors diverse niches colonized by microbes collectively termed cutaneous microbiota (CM). Previous studies have confirmed that CM interacts closely with the immune system,[6] with implications for various immune-associated skin diseases, including psoriasis, atopic dermatitis (AD), and BP.[24] However, research on CM in pemphigus is relatively scarce. A pilot study showed significant changes in the CM composition of lesion sites[25] demonstrating reduced alpha diversity (indicating reduced richness and uniformity). Firmicutes phylum and *Staphylococcus* genus, specifically *Staphylococcus epidermidis* and *Staphylococcus aureus*, demonstrated the highest relative abundance, suggesting a possible role of Firmicutes phylum in the pathogenesis of AIBDs.

S. epidermidis is a dominant group in healthy CM, playing a dual role in both symbiosis and pathogenesis, as observed in AD.[26] Especially under immunosuppressed conditions, it may transition into an opportunity pathogen.[25] Its pathogenic potential is mediated by extracellular cysteine protease A (EcpA), a key virulence factor secreted by this bacterium.[27,28] Studies have shown that the abundance of *S. epidermidis* positively correlates with EcpA transcript levels in lesional skin of both Netherton syndrome and AD.[27,28] EcpA contributes to skin barrier dysfunction by cleaving critical structural components, including Dsg1 and the antimicrobial peptide (AMP) LL-37, thereby increasing susceptibility to pathogenic invasion and secondary infections.[28]

S. aureus, a major human pathogen, is involved in various inflammatory skin diseases, including AD, psoriasis, BP, and cutaneous infections.[11,29,30] It damages cutaneous tissue through the V8 protease-PAR1 axis[31] and additionally disrupts skin integrity by secreting virulent factors (such as exotoxins, proteases, and superantigens), which subsequently triggers inflammatory responses.[32] Furthermore, *S. aureus* is the most prevalent bacterium in secondary infections among both PV and BP patients, with its presence significantly correlating with poor clinical outcomes.[33,34] More importantly, the ability to form biofilms on the skin surface and evade the host immune system facilitates its persistent colonization and chronic infections.[35,36] Collectively, these findings suggest that *S. aureus* is involved in the pathogenesis and progression of PV.

Oral Microbiota

Approximately 90.3% of PV patients experience oral erosive lesions, which may occur with or without cutaneous/mucosal involvement, making the oral mucosa the most frequent disease onset site.[37] Oral mucosal erosions are presented predominantly in the buccal mucosa, palate, and tongue,[1] while gingiva involvement is less common.[38] The oral cavity is colonized by a diverse array of microorganisms known as the oral microbiota (OM), which establish distinct microbial communities at different colonization sites, including the oral mucosa, tooth surfaces, and saliva.[39]

Compared to HCs, patients with PV exhibit higher alpha diversity and significantly different beta diversity, reflecting distinct microbial community composition.[39] At the genus level, *Prevotella* was enriched in PV patients and showed a remarkable correlation with serum anti-Dsg3 levels, while *Neisseria* was decreased and correlated with serum anti-Dsg1 levels.[39,40] These observations indicate that *Prevotella* and *Neisseria* may play a role in PV pathogenesis. Mechanistically, *Prevotella* may promote skin damage primarily by Toll-like receptor (TLR) 2-mediated activation of antigen-presenting cells, which secrete Th17-polarizing cytokines, including interleukin (IL)-6, IL-1, and IL-23.[41,42] Additionally, *Prevotella* induces epithelial cells to produce pro-inflammatory factors such as IL-8, IL-6, and CCL20, which amplify Th17 responses and enhance neutrophil recruitment, further exacerbating tissue damage.[41]

In the *Neisseria* genus, *Neisseria subflava* and *Neisseria sicca*, predominant in the healthy OM, competitively inhibit the growth of pathogenic microorganisms, maintaining oral health.[43] Similarly, *Streptococcus*, the most prevalent genus

in the oral environment in both HCs and PV groups, shows an increased trend in PV patients.[39] In addition, *Agrobacterium* shows remarkably higher relative abundance in PV saliva than in HCs, while *Lautropia* and *Fusobacterium* exhibit significantly lower levels.

Malodor (halitosis), one of the symptoms troubling patients with AIBDs, is related to OM composition.[44] Research has revealed that PV patients show an increased abundance of bad-breath-related species (mainly *Fusobacterium nucleatum* and *Parvimonas micra*) and decreased abundance of clean-breath-related species (ie *Streptococcus salivarius* and *Rothia mucilanginosa*).[39] Interestingly, different sampling sites yielded different results. For instance, *Fusobacterium* genus increases in PV oral lesions but decreases in saliva, whereas *Prevotella* shows the reverse pattern.[39,40]

Bullous Pemphigoid

Gut Microbiota

A multicenter case-control study on BP reported a reduction in alpha diversity and notable alterations in beta diversity among newly diagnosed and relapsed cases.[45] Compared to HCs, several beneficial bacteria were decreased in BP patients, including Lachnospiraceae, *Faecalibacterium*, and *B. ovatus*.[14,46] Conversely, some potentially pathogenic bacteria were enriched, such as *Bacteroides eggerthii, E. coli, Prevotella copri*, and *Flavonifractor plautii*.[45,46]

The Lachnospiraceae family, abundant in healthy individuals, contributes to host health by participating in SCFAs production, bile acids conversion, and enhancing resistance to intestinal pathogens colonization.[47] *Faecalibacterium*, a beneficial genus with important health benefits, exerts robust anti-inflammatory effects through multiple mechanisms: promoting the suppressive response of Foxp3+ Treg cells, boosting the secretion of the anti-inflammatory cytokine IL-10 from antigen-presenting cells and Treg cells, and directly producing microbial anti-inflammatory molecules.[48] In addition, several members of this genus are SCFAs-producing bacteria that strengthen intestinal barrier and reduce permeability to pathogens and antigens.[22] Notably, *F. Prausnitzii* (the dominant species in HCs) is significantly decreased in BP patients, highlighting its crucial role in disease pathogenesis.[14,45] *B. ovatus* is also a beneficial bacterium that can produce SCFAs and stimulate the secretion of gut IgA, the most abundant mucosal antibody that plays a vital role in restricting the colonization and invasion of bacteria and bacterial toxins, thereby maintaining gut homeostasis.[49,50] More importantly, it has been identified as the species that best elicits intestinal IgA production via T cell-dependent B cell activation.[51]

The potentially pathogenic bacterium *B. eggerthii* is elevated in BP patients and positively correlated with the neutrophil-to-lymphocyte ratio which is positively associated with the disease activity of BP.[51,52] *E. coli*, some serotypes of which are pathogenic, also displays a high positive correlation with BP disease severity.[45] *P. copri* is a complex gut microorganism with dual roles in immunity. It exerts anti-inflammatory effects by producing SCFAs.[53] However, it can also initiate and exacerbate inflammation by enhancing Th17 immune responses by upregulating Th17-related cytokines, including IL-1β and IL-23 from antigen-presenting cells, as well as IL-6, IL-8, and CCL20 from epithelial cells.[41,54] Another dual-functional bacterium, *F. plautii* also demonstrates both anti-inflammatory (via inhibition of Th2 immune response, TNF-α expression, and IL-17 signaling) and pro-inflammatory (via quercetin cleavage) activities, with significant links to BP relapse.[45,55–58] Provided its diverse functions, further research is needed to fully understand the contribution of *P. copri* and *F. plautii* to BP pathogenesis.

The GM composition shifts significantly between active and remission disease stages. During active phases, Lachnospiraceae abundance decreases while Ruminococcaceae and Bacteroidaceae increase, and patterns are reverse during remission.[46] Notably, while Lachnospiraceae maintains gut homeostasis in healthy individuals,[47] pathogenic Bacteroidaceae members (such as *B. eggerthii*,[45] *B. kribbi*,[46] *B. caccae*[14]) become are enriched in patients with BP. These GM alteration patterns mirror those seen in inflammatory bowel disease,[59] which shares clinical associations with BP,[60] implying that GM may play a more substantial role in BP pathogenesis than previously recognized.

Cutaneous Microbiota

Similar to PV, research on CM in BP remains limited, with only three studies available. A significant reduction in alpha diversity was observed at both lesional and BP-susceptible sites (including perilesional and contralateral non-lesional areas).[11] Beta diversity also differed between patients and controls at perilesional sites, as well as between perilesional and non-lesional sites in patients.[11,61] The three existing studies consistently reported *Staphylococcus* as the most

abundant genus on lesional sites, with three main species: *S. epidermidis, S. aureus*, and *S. hominis*.[11,25,61] However, findings are inconsistent regarding the predominant species, with one study identifying *S. epidermidis* as the primary strain, while others report *S. aureus* as the dominant pathogen.[11,25,61]

As mentioned above, *S. epidermidis* is a dominant commensal bacterium on healthy skin, where it contributes to microbial homeostasis but can act as an opportunistic pathogen under immunosuppression.[25] *S. aureus* is markedly abundant in BP-susceptible sites and positively correlated with disease severity.[11,25] In random forest classification analysis, *S. aureus* Amplicon Sequence Variant (ASV) _2 is the top ASV for distinguishing BP patients from HCs.[11] Beyond inducing skin inflammation and barrier dysfunction, *S. aureus* is implicated in triggering itch, a hallmark BP symptom, and the resulting scratching behavior potentially exacerbates *S. aureus* colonization and proliferation, creating a feedback loop that amplifies bacterial load.[31] Conversely, the commensal bacterium *S. hominis* is negatively correlated with disease severity at BP-susceptible sites.[11] These findings highlight the intricate interplay between skin microbial communities and BP pathogenesis.

As the second most abundant species in BP-perilesional areas, *Cutibacterium acnes* displayed reduced abundance and was identified as a BP biomarker.[11] Although involved in acne development, it exhibits protective functions in healthy skin by secreting antimicrobial compounds, hydrolyzing triglycerides, and generating SCFAs.[62] Furthermore, *C. acnes* ASV_1 showed an inverse correlation with *S. aureus* ASV_2 at all sampling sites in BP groups, indicating a potential antagonism between these two species.[11] These findings reveal complicated microbiota interactions in BP progression and highlight the potential protective role of *C. acnes*.

Oral Microbiota

BP lesions predominantly affect limb flexures and the abdomen, with oral mucosal involvement occurring in ~15% of cases.[63] Only one study has examined OM alterations in BP patients due to limited oral mucosa samples,[25] revealing Firmicutes as the predominant phylum.

MMP, a subtype of pemphigoid diseases, primarily involves mucous membranes, with the oral cavity, particularly the gingiva and buccal mucosa, which are the most involved sites.[1] The gingival manifestation of MMP is also known as Desquamative Gingivitis. Elevated levels of subgingival colonization by *Eikenella corrodens, F. nucleatum*, and *Capnocytophaga spp*. were observed in patients with MMP compared to control individuals with plaque-induced gingivitis.[64]

Notably, the proteomes of *E. corrodens* and *F. nucleatum* share multiple heptapeptides with the BP180 and BP230.[65] Given that the likelihood of two proteins sharing a heptapeptide is extremely low (1 in 1.28 billion), this overlap is unlikely to be coincidental. These findings suggest that infections with *E. corrodens* and *F. nucleatum* may potentially trigger or exacerbate autoimmune responses in MMP through molecular mimicry mechanisms.

Collectively, these findings highlight significant alterations in the gut, skin, and oral microbiota of patients with AIBDs, as summarized in Table 1. Key microbial shifts at different taxonomic levels may serve as potential biomarkers or therapeutic targets. Further, the functional roles of these microbiota in disease pathogenesis are detailed in Table 2, providing a mechanistic basis for their implications in AIBDs susceptibility and progression, which will be discussed in the following section.

Distinct Gut Microbial Signatures in AIBDs Amidst Shared Dysbiosis

Mounting evidence has elucidated the pivotal role of microbial dysbiosis in the pathogenesis of diverse inflammatory skin conditions, including but not limited to psoriasis, AD, acne vulgaris, rosacea, alopecia areata, and hidradenitis suppurativa.[12] Nevertheless, delineating disease-specific microbial signatures continues to pose considerable challenges due to the intricate host-microbe interactions. Notably, AIBDs exhibit both GM changes with other inflammatory skin disorders, and distinctive microbial profiles which may be intrinsically linked to their autoimmune targeting of adhesion molecules. This section systematically synthesizes current evidence regarding several representative bacterial genera and species implicated in these processes.

The genus *Faecalibacterium* demonstrates markedly reduced abundance in psoriasis,[72] acne vulgaris,[72] pemphigus,[17] and BP,[14] while demonstrating significant enrichment in AD.[73] Its hallmark species, *F. prausnitzii*, follows a similar trend, with increased colonization in AD[73] but diminished presence in hidradenitis suppurativa,[74] pemphigus,[17] and

Table 1 Alterations or Characteristics of Microbiota in AIBDs

Gut			Skin			Oral		
Taxon	**Pemphigus**	**BP**	**Taxon**	**Pemphigus**	**BP**	**Taxon**	**Lesions**	**Saliva**
Firmicutes	↓[17]	↓[14,46]	**Firmicutes**	MA[25]	MA[11,25,61]	**Firmicutes**	MA;↑[39]	–
└Ruminococcaceae	↓[17]	↑[46]	└Staphylococcaceae	MA[25]	MA[11,25,61]	└Streptococcaceae	MA;↑[39]	–
└ └*Faecalibacterium*	↓[17]	↓[14]	└ └*Staphylococcus*	MA[25]	MA[11,25,61]	└ └*Streptococcus*	MA;↑[39]	–
└ └ └*prausnitzii*	↓[17]	↓[14,45]	└ └ └*epidermidis*	AS[25]	AS[61]	└ └ └*salivarius*	↓[39]	–
└ └*Flavonifractor*	–	↑[45]	└ └ └*aureus*	AS[25]	AS[11,25]	└Peptoniphilaceae	–	–
└ └ └*plautii*	↑[15]	↑[45]	└ └ └*hominis*	–	↓[11]	└ └*Parvimonas*	–	–
└Lachnospiraceae	↓[15,17]	↓[46]				└ └ └*micra*	↑[39]	–
└ └*Roseburia*	↓[17]	–	**Actinobacteria**	–	–			
└ └ └*intestinalis*	↓[17]	–	└Propionibacteriaceae	–	–	**Bacteroidetes**	↓[39]	–
└ └*Coprococcus*	↓[15]	–	└ └*Cutibacterium*	–	–	└Prevotellaceae	↓[39]	–
└Carnobacteriaceae	↑[15]	–	└ └ └*acnes*	–	↓[11]	└ └*Prevotella*	↓[39]	↑[40]
└ └*Granulicatella*	↑[15]	–				└ └ └*spp.*	–	↑[40]
						└Fusobacteriaceae	↑[39]	–
Proteobacteria	↑[14,16–18]	–				└ └*Fusobacterium*	↑[39]	↓[40]
└Enterobacteriaceae	↑[17]	–				└ └ └*nucleatum*	↑[39]	–
└ └*Escherichia*	↑[17,18]	↑[45]/↓[14]						
└ └ └*coli*	↑[17,18]	↑[45]				**Proteobacteria**	↑[39]	–
└*Shigella*	↑[17]	–				└Neisseriaceae	↓[39]	–
└ └*Klebsiella*	↑[17,18]	↓[14]				└ └*Neisseria*	–	↓[40]
└ └ └*pneumoniae*	↑[17]	–				└ └ └*Perflava*	↓[39]	–
└ └*Enterobacter*	–	–						
└ └ └*hormaechei*	↑[17]	–				**Actinobacteria**	↓[39]	↓[40]
						└Micrococcaceae	–	–
Bacteroidetes	↓[18]/↑[16]	↑[14]				└ └*Rothia*	–	↓[40]
└Bacteroidaceae	–	↑[46]				└ └ └*mucilanginosa*	↓[39]	–
└ └*Bacteroides*	↑[17]	↑[14]						
└ └ └*ovatus*	↓[18]	↓[46]						
└ └ └*uniformis*	↓[18]	–						
└ └ └*fragilis*	↑[17]	–						
└ └ └*eggerthii*	–	↑[45]						
└ └ └*kribbi*	–	↑[46]						
└ └ └*caccae*	–	↑[14]						
└Prevotellaceae	↓[16]	↓[46]						
└ └*Prevotella*	↓[16]	↑[14]						
└ └ └*copri*	↓[16]	↑[46]						

Notes: The microbiota are classified into four taxonomic hierarchies (phylum-family-genus-species): Phylum: bolded for emphasis; Family: prefixed with "└"; Genus: prefixed with "└ └"; Species: prefixed with "└ └ └". Symbols: ↑: The abundance of phylum/family/genus/species increases; ↓: The abundance of phylum/family/genus/species decreases; -: Not reported.

Abbreviations: MA, most abundant; AS, advantage species.

Table 2 Detailed Description of the Altered Species in AIBDs

Sites	Species	Attribute	Functions	Mechanisms	References
Gut	*Faecalibacterium prausnitzii*	Beneficial	Strengthen intestinal barrier; Anti-inflammation; Reduce auto-antibody	Produce SCFAs	[17]
	Flavonifractor plautii	Dual	Pro-inflammatory	Cleave quercetin, which has anti-oxidant and anti-inflammatory properties	[58]
			Anti-inflammation	Inhibit Th2 immune response, TNF-α expression and IL-17 signaling	[55–57]
	Roseburia intestinalis	Beneficial	Strengthen intestinal barrier; Anti-inflammation; Reduce auto-antibody	Produce SCFAs	[17]
	Escherichia coli	Potentially pathogenic	Impair intestinal barrier; Pro-inflammation;	Produce LPS	[18]
	Klebsiella pneumoniae	Potentially pathogenic	Impair intestinal barrier; Pro-inflammation	Produce LPS	[18]
			Induce auto-immunity	Cross-reactivity and molecular mimicry	[16]
	Enterobacter hormaechei	Potentially pathogenic	Impair intestinal barrier; Pro-inflammation	Produce LPS	[18]
	Bacteroides ovatus	Beneficial	Strengthen intestinal barrier; Anti-inflammation; Reduce auto-antibody	Produce SCFAs	[18]
			Maintain gut homeostasis	Drive gut IgA production	[50]
	Bacteroides uniformis	Beneficial	Strengthen intestinal barrier; Anti-inflammation; Reduce auto-antibody	Produce SCFAs	[18]
			Maintain gut homeostasis	Degrades β-glucan into nicotinamide	[66]
			Strengthen intestinal barrier; Anti-inflammation;	Modulate intestinal bile acid metabolism	[67]
	Bacteroides fragilis	Potentially pathogenic	Impair intestinal barrier; Pro-inflammation	Produce LPS	[18]
			Impair intestinal barrier; Pro-inflammation	Produce Bacteroides fragilis toxin	[68]
	Prevotella copri	Dual	Impair intestinal barrier; Pro-inflammation	Produce LPS; Promote Th17 immune responses	[16,41,54]
			Strengthen intestinal barrier; Anti-inflammation; Reduce auto-antibody	Produce SCFAs	[69]
Skin	*Staphylococcus epidermidis*	Dual	Impair cutaneous barrier; Promote pathogens	Secret EcpA	[27,28]
			Inhibit pathogens	Produce extracellular serine protease; Promote keratinocytes to produce AMP	[70]
	Staphylococcus aureus	Pathogenic	Impair cutaneous barrier; Pro-inflammation; Intrigue itch Induce infections	Produce various exotoxins and proteases	[31–34]
	Staphylococcus hominis	Beneficial	Inhibit pathogens	Produce lantibiotics	[70]
	Cutibacterium acnes	Dual	Promote *S. aureus*	Produce coproporphyrin III	[71]
			Inhibit *S. aureus*	Produce SCFAs and antimicrobial compounds	[62]

(*Continued*)

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Table 2 (Continued).

Sites	Species	Attribute	Functions	Mechanisms	References
Oral	*Streptococcus salivarius*	Beneficial	Freshen breath	-	[39]
	Parvimonas micra	Adverse	Promote halitosis	-	[39]
	Neisseria perflava	Commensal	-	-	[39]
	Rothia mucilanginosa	Beneficial	Freshen breath	-	[39]
	Fusobacterium nucleatum	Adverse	Promote halitosis	-	[39]

Notes: -: not reported.

BP.[14,45] Notably, *F. prausnitzii* exhibits a positive correlation with anti-Dsg1 and anti-Dsg3 antibody titers,[16] established serological markers of pemphigus disease activity.

The genus *Prevotella*, particularly species *P. copri*, displays reduced prevalence in rosacea[75] and pemphigus,[16] yet is elevated in BP.[14,46] Intriguingly, studies report discordant associations between *Prevotella* and pemphigus autoantibodies: while positively associated with anti-Dsg1,[16] it inversely correlates with anti-Dsg3,[17] suggesting antibody-specific microbiota interactions.

E. coli manifests increased abundance in psoriasis,[76] pemphigus,[17,18] and BP,[45] with a strong positive correlation to BP severity as quantified by the Bullous Pemphigoid Disease Area Index score,[45] implicating it as a potential biomarker for progressive disease.

Collectively, these microbiota-dermatosis associations underscore critical knowledge gaps, emphasizing the urgent need for cross-disease comparative studies to elucidate microbiome-driven mechanisms in cutaneous pathophysiology.

Implications of the Microbiota for AIBDs Susceptibility and Progression

Gut–Skin Axis

Emerging evidence underscores the intricate interactions between gut and skin, wherein GM influences cutaneous pathophysiology through two key systems: neural and immune pathways.[12] GM-derived neurotransmitters [such as γ-aminobutyric acid (GABA), acetylcholine, dopamine, and serotonin] modulate cutaneous conditions. Meanwhile, microbial metabolite dysbiosis (mainly SCFAs and LPS) may induce local inflammation and translocation across compromised intestinal barriers, thereby triggering systemic immune responses. This relationship is termed as the gut-skin axis, as shown in Figure 1.

Short Chain Fatty Acids (SCFAs)

SCFAs, predominantly acetate, propionate, and butyrate, are well-documented for their ability to strengthen intestinal barrier integrity and maintain intestinal homeostasis.[22] Produced by GM—primarily Firmicutes and Bacteroidetes—from fermentation of indigestible dietary fiber, SCFAs are partially absorbed by colonocytes for energy production (ATP), while the remainder enters circulation and exerts systemic effects by activating G-protein coupled receptors (GPR), such as GPR41, GPR43, and GPR109A, which are expressed in various tissues (intestinal epithelial cells, adipocytes, and immune cells).[77,78] Additionally, SCFAs can directly inhibit histone deacetylase (HDAC), thereby epigenetically modulating gene expression.[78] Here, we highlight the immunomodulatory properties of SCFAs, which help alleviate dermatological disorders resulting from immune system dysregulation.[79]

In mononuclear cells, SCFAs, especially butyrate, suppress the nuclear factor kappa-B (NF-κB) signaling pathway and TNF-α secretion, which are involved in the inflammatory response.[80] Notably, NF-κB activation enhances TNF-α production, while TNF-α, through its receptor TNFR, activates downstream signaling pathways that subsequently amplify NF-κB activation, establishing a positive feedback loop.[81] In macrophages, butyrate acts as an HDAC inhibitor to reduce the production of pro-inflammatory cytokines, such as TNF-α, MCP-1, and IL-6.[82]

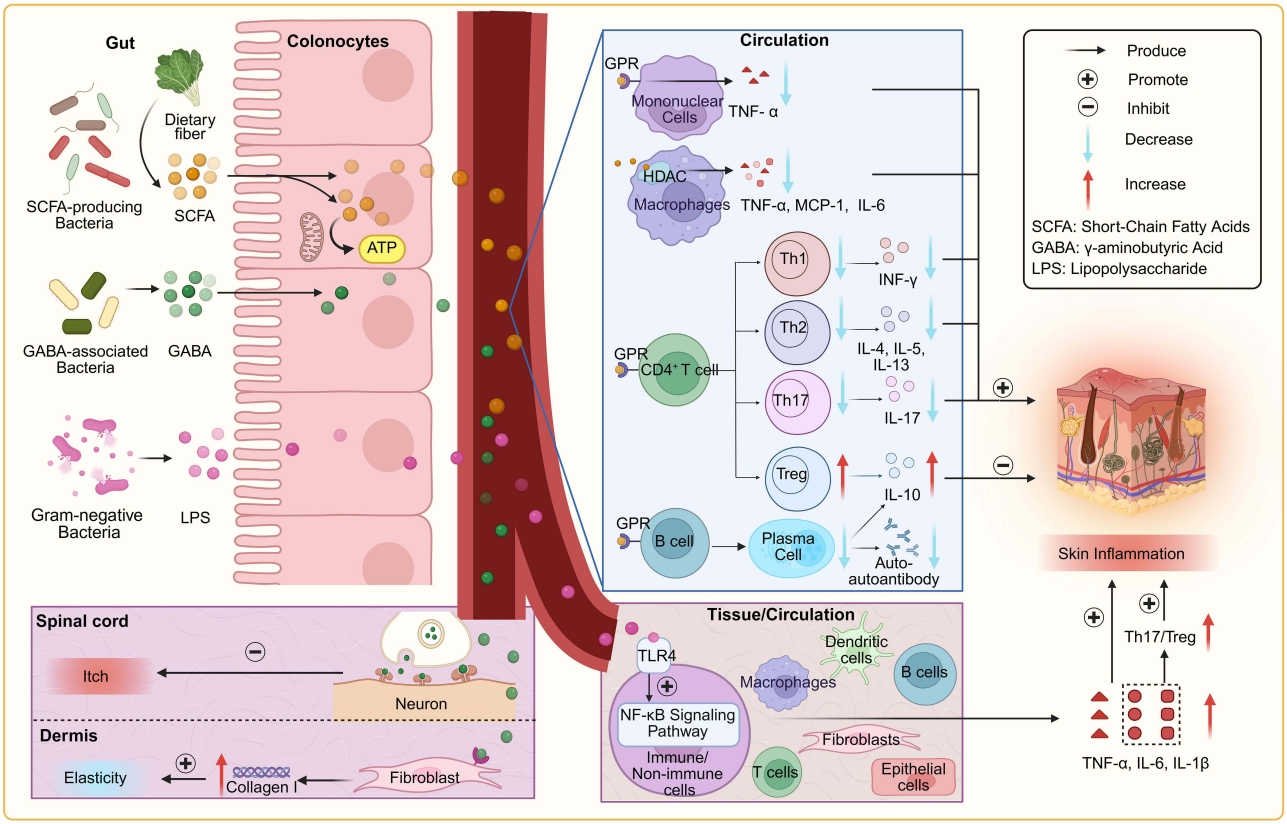

Figure 1 Gut-Skin axis mediated by gut microbiota. This illustration represents the underlying mechanisms by which GM modulate skin inflammation through three primary mediators: SCFAs, GABA, and LPS. Dietary fiber is fermented by SCFAs-producing bacteria to generate SCFAs that are partially absorbed by colonocytes for ATP production, while the remainder enters circulation to modulate immunity via GPR signaling and HDAC inhibition. SCFAs reduce TNF-α secretion in mononuclear cells, suppress inflammatory cytokines in macrophages, and inhibit Th1, Th2, and Th17 differentiation, thereby decreasing IFN-γ, IL-4, IL-5, IL-13, and IL-17 levels, while enhancing Treg cell differentiation and IL-10 expression. Overall, these metabolites lower pro-inflammatory factors and boost anti-inflammatory responses. Additionally, SCFAs also dampen plasma cell differentiation and autoantibody production. GABA-associated bacteria synthesize GABA, which is transported by colonocytes into circulation to exert systematic effects. It alleviates itch by inhibiting spinal neurons and enhances skin elasticity by increasing collagen I levels in dermal fibroblasts. LPS from the cell walls of gram-negative bacteria, activates the LPS/TLR4/NF-κB signaling pathway in immune cells and non-immune cells, triggering pro-inflammatory factors like TNF-α, IL-6, and IL-1β. Among these, IL-6 and IL-1β increase the Th17/Treg balance, further promoting skin inflammation. This illustration was created with BioRender.com.

In T cells, SCFAs suppress Th1 and Th2 cell differentiation and related cytokines production such as IFN-γ, IL-4, IL-5, and IL-13, while promoting Treg cell differentiation, Foxp3+ Treg cells and IL-10 suppressive activity.[48,83] Valerate specifically inhibits Th17 responses by reducing IL-17 production and downregulating Th17-associated gene expression.[84] In B cells, butyrate and propionate attenuate both intestinal and systemic plasma cell differentiation and autoantibody production via HDAC inhibition, as evidenced by lower IgG1, IgA, and IgE levels in SCFAs-fed mice.[85] Valerate also boosts IL-10 production in both B and CD4+ T cells.[48] Notably, SCFAs have been proven to inhibit autoantibody production and autoimmunity in mouse lupus models.[85] All of the aforementioned evidence indicates that SCFAs have the potential to modulate immune response, thereby offering therapeutic benefits against autoimmune diseases.

F. prausnitzii and *R. intestinalis* from the Firmicutes Phylum, as well as *B. ovatus* and *B. uniformis* from the Bacteroidetes phylum are SCFAs-producing bacteria consistently reduced in both PV and BP. Furthermore, SCFAs-targeted metabolomics analysis revealed elevated levels of GM-derived SCFAs in PV patients after glucocorticoid treatment,[18] suggesting that GM dysbiosis may disrupt skin health in blistering diseases through SCFAs-mediated immunological crosslinking.

γ-Aminobutyric Acid (GABA)

GABA, a low-molecular-weight metabolite, is transported into circulation through colonocytes, contributing to plasma GABA levels.[86] Importantly, germ-free mice displayed markedly reduced GABA levels in both stool and blood,[86] revealing that GM can manipulate the plasma levels of GABA.

Metagenomic shotgun sequencing demonstrated that, in BP patients, the GABA shunt and related pathways are enriched and positively correlated with disease severity.[45] These pathways involve the biosynthesis of pyridoxal 5'-phosphate (a key cofactor for glutamate-to-GABA conversion) and putrescine (GABA precursor),[45] suggesting increased microbial-derived GABA in the gut of BP patients. Moreover, *E. coli*, the predominant species associated with these pathways, increases in BP patients and displays the strongest correlation with disease severity,[45] further supporting the importance of the GABA shunt in BP pathophysiology. Consistent with this, stool transcriptomics from healthy subjects demonstrated active GABA pathway expression in *Bacteroides spp*. (particularly *B. fragilis*) and *Escherichia spp*. (especially *E. coli*), both of which were consistently enriched in the GM of PV and BP patients.[14,17,45,87]

Interestingly, the inhibitory neurotransmitter GABA is regarded as a protective factor for skin health by suppressing itch via inhibition of spinal itch-signaling neurons,[88] while simultaneously maintaining skin elasticity through upregulating type I collagen expression and inhibiting its degradation in dermal fibroblasts.[89] However, clinical observations in AD reveal a paradoxical association, where GABA degradation correlates with symptom improvement, while its biosynthesis from putrescine is associated with disease severity,[90] suggesting potential detrimental effects of microbial-derived GABA on AD patients. This paradox is further complicated by experimental evidence showing that both oral GABA and intraperitoneal GABA receptor agonists can ameliorate AD-like lesions and pruritus in mouse models.[91,92] These contradictory findings warrant further investigation into GM-mediated GABA metabolism, tissue-specific GABA distribution, and GABA signaling pathways in AIBDs.

Lipopolysaccharide (LPS)

LPS, a gram-negative bacterial endotoxin, potently activates the LPS/TLR4/NF-κB pathway in both immune (macrophages, dendritic cells, B cells, and specific T cell subsets) and non-immune cells (fibroblasts and epithelial cells), triggering the secretion of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β.[93] Notably, these cytokines are elevated in BP blister fluid and PV serum, where they promote Th17/Treg imbalance through Treg suppression and Th17 activation.[15,94,95] Supporting this mechanism, in vitro studies demonstrated that *E. coli* LPS exacerbates inflammation in oral lichen planus via the same pathway.[96]

Accumulating evidence has proven that T cell subset abnormalities, particularly Th1/Th2 and Th17/Treg imbalance, plays a pivotal role in the initiation and development of AIBDs.[4] The Th1 response, characterized by interferon-gamma (IFN-γ) production, promotes inflammation, while Th2 cytokines (IL-4, IL-5, IL-13) stimulate B cell activation and antibody production.[4] Th17 cells mediate inflammation and tissue damage through IL-17 secretion, whereas Treg cells suppress autoreactive T cell proliferation and antibody production via IL-10 and transforming growth factor-beta.[97] In PV serum, Th1 and Treg levels decrease while Th2 and Th17 increase, a pattern similarly observed in BP, except for Th1 cells, which have not been clearly reported.[4,15]

Collectively, these results suggest that LPS are likely to contribute to the pathogenesis of AIBDs by initiating and sustaining an inflammatory milieu via the LPS/TLR4/NF-κB signaling pathway and T cell subset imbalance.

Cutaneous Microbiota-Host Interactions

The interaction between CM and the host is complex, encompassing both mutualism and pathogenicity within the context of health and disease, with microbial metabolism and immune modulation serving as key mechanistic links.[98] *Propionibacterium* and *Staphylococcus* are the two most common genera on healthy skin with *C. acnes* (formerly *P. acnes*) and *S. epidermidis* being the most representative species, respectively.[70] These commensal bacteria exhibit adverse effects on the host under certain conditions, displaying different relative abundance at the lesional sites of pemphigus and BP compared to HCs.[11,25,61] In contrast, the pathogenic *S. aureus*, a known biofilm-forming colonizer, is markedly enriched in these AIBDs.[11,25,61] In general, *S. aureus* and three others show the strongest disease associations, as depicted in Figure 2.

S. aureus

S. aureus directly injures cutaneous tissues and triggers inflammation by producing virulence factors (exotoxins and proteases).[32] *S. aureus* exotoxins are classified into three main groups: exfoliative toxins, membrane-damaging toxins,

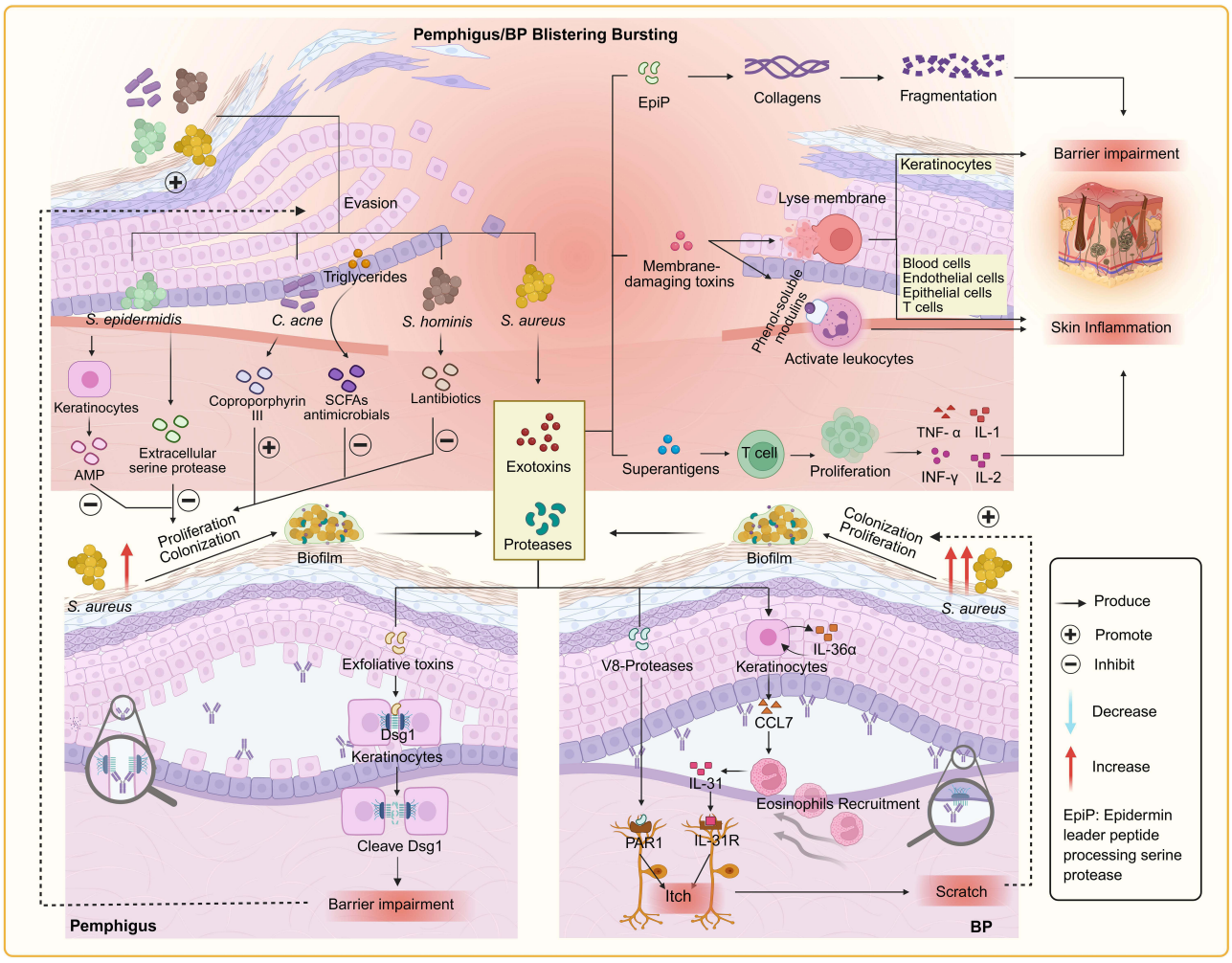

Figure 2 Interactions between cutaneous microbiota and host. The figure depicts four clinically relevant cutaneous microbiota species in pemphigus and BP: *S aureus, S. epidermidis, C. acnes*, and *S. hominis*. The upper figure illustrates the potential microbial mechanisms shared by pemphigus and BP, while the lower figures elaborate on the specific effects of S. aureus on two diseases respectively. *S. aureus*, which is significantly enriched in the skin lesions of pemphigus and BP, damages the skin barrier and triggers inflammation by producing exotoxins and proteases. Especially when blisters rupture, more bacterial invasion into the dermis, causing more extensive inflammatory responses. Exotoxins are categorized into exfoliative toxins, membrane-damaging toxins, and superantigens. Exfoliative toxins disrupt keratinocyte connections (Dsg1). Membrane-damaging toxins lyse the membrane of various cell types, including keratinocytes, blood cells, endothelial cells, epithelial cells, and T cells, and initiate pro-inflammatory responses in leukocytes, further exacerbating inflammation. Superantigens polyclonally spur large populations of T cells, resulting in the extensive secretion of cytokines, including TNF-α, IL-1, IL-2, IFN-γ. *S. aureus* proteases degrade collagen and keratinocyte connections (Dsg1), effectively undermining skin barrier function. In BP, *S. aureus* proteases are implicated in triggering itch through the V8 protease-PAR1 axis and eosinophil recruitment. The other three species influence *S. aureus* proliferation through various mechanisms. *S. epidermidis* inhibits *S. aureus* by producing extracellular serine protease and enhancing AMP production from keratinocytes. *C. acnes* produce coproporphyrin III to promote *S. aureus* aggregation, yet counteracts its growth by generating SCFAs through triglyceride fermentation. *S. hominis* produces antibiotics to resist S. aureus colonization. This illustration was created with BioRender.com.

and superantigens.[99] Exfoliative toxins are specific serine proteases that cleave the connections between keratinocytes and intercellular adhesion, including Dsg1, causing skin desquamation and blister formation.[100] The membrane-damaging toxins, falling into three key groups: hemolysins, leukocidins, and phenol-soluble modulins, are capable of lysing a variety of cell types, such as multiple blood cells, epithelial cells, endothelial cells, keratinocytes, and T cell.[99] Besides, phenol-soluble modulins can bind to pattern recognition receptor formyl peptide receptor 2, initiating a cascade of pro-inflammatory responses in leukocytes.[101]

Superantigens polyclonally spur large populations of T cells, leading to excessive secretion of cytokines (TNF-α, IL-1, IL-2, IFN-γ) which mediate bacterial toxic effects.[99] Notably, these cytokines are elevated in the blister fluid of BP patients, and IL-1β and IL-2R are increased in PV plasma.[15] Specific IgE antibodies to *S. aureus* superantigens are present in the serum of BP patients and may exacerbate clinical symptoms, as evidenced by the higher mean Bullous

Pemphigoid Disease Area Index values in sensitized individuals.[102] The predominant *S. aureus* superantigens include staphylococcal exotoxins and Staphylococcal toxic shock syndrome toxin-1.[103]

Generally, *S. aureus* exotoxins activate both innate and adaptive immune responses, driving skin inflammation. This is especially pronounced when the skin barrier is compromised, which facilitates bacteria to invade from the epidermis to the dermis, amplifying inflammatory responses.[70] Beyond exotoxins, *S. aureus* secretes various proteases that cleave key components of skin structure, including extracellular matrix and intercellular junctions, as well as vital elements of the innate immune system, such as the complement system, effectively undermining skin integrity and barrier function.[104] Specifically, the mechanism of *S. aureus* proteases inducing eosinophil recruitment via IL-36R signaling has been clearly established.[105] Unlike PV, eosinophils are the predominant infiltrating cells in BP lesions, which are responsible for skin inflammation and anti-BP180 IgE-mediated skin blistering.[1] In BP, eosinophils are the major source of IL-31,[106] which is elevated in BP lesions and peripheral nerves (with higher IL-31RA expression) compared to PV,[107] suggesting the IL-31/IL-31RA pathway and eosinophils may contribute to the pruritus in BP. Additionally, *S. aureus* triggers pruritus and scratch-induced skin damage through the V8 protease-PAR1 axis.[31]

Although *S. aureus* increases in both PV and BP compared to HCs, the relative abundance of this bacterium is notably higher in patients with BP,[25] which may offer valuable insights into the pruritus associated with BP.

Other Species

S. epidermidis is primarily a mutualistic bacterium but becomes an opportunistic pathogen during immunosuppression or barrier breach, turning into a target for the immune system.[25,70] It inhibits *S. aureus* growth and biofilm formation by producing extracellular serine protease and promotes keratinocytes to produce AMP which effectively combat pathogens.[70] Conversely, *S. epidermidis* also degrades the skin barrier and AMP LL-37 through secreting EcpA protease.[27,28]

Current evidence regarding *C. acnes* in AIBDs remains limited, with only one study reporting its decreased abundance in BP patients.[11] However, emerging evidence reveals complex interspecies interactions between *C. acnes* and *S. aureus*. *C. acnes* produces coproporphyrin III to promote *S. aureus* aggregation and biofilm formation,[71] while in another study, *C. acnes* is regarded as a probiotic that resists *S. aureus* by producing SCFAs antimicrobials through triglycerides fermentation.[62]

S. hominis produces lantibiotics that synergize with the human antimicrobial peptide LL-37 to resist *S. aureus* colonization.[70]

Given the paucity of research on CM changes and functions in AIBDs, coupled with inconsistent findings in existing studies, further research is essential to clarify the CM-AIBDs relationship and offer new insights into pathogenesis and therapeutic strategies.

Oral Microbiota-Host Interactions

In AIBDs, oral mucosal involvement is prominent in both PV and MMP, though MMP itself has a relatively low incidence.[108] MMP predominantly affects the gingiva, manifesting as Desquamative Gingivitis, whereas PV primarily targets oral regions other than gingiva.[38] Studies have revealed dysbiosis of OM in both PV and MMP, possibly initiating and perpetuating disease process.[25,39,40,65]

As previously noted, in the saliva of PV patients, the relative abundance of Prevotella is significantly increased and positively correlated with PV-related factor (serum anti-Dsg3) levels.[40] Analogous results were observed in rheumatoid arthritis, another prevalent autoimmune disorder.[109] In patients with MMP, several species exhibit a significant increase and share multiple heptapeptides with BP180 and BP230, indicating that OM may trigger autoimmune responses through cross-reactivity.[65]

Moreover, oral lesions impair oral hygiene and facilitate pathogenic anaerobic bacterial overgrowth in dental and periodontal areas, leading to dental plaque formation and periodontal disease development.[110] Reciprocally, periodontal diseases caused by OM dysbiosis may constitute a potential risk factor for AIBDs through immune mechanisms, such as molecular mimicry and Th17 cell differentiation.[111]

In conclusion, the pathogenesis of AIBDs is influenced by both autoimmunity and periodontal diseases, which may mutually exacerbate each other.

Potential Application of Microbiota Regulation in AIBDs

Host Microbiota and AIBDs Prognosis

Although there is no direct evidence linking specific bacterial species to AIBD onset, studies have consistently associated alterations in the host microbiota with disease progression and prognosis. Moreover, the relative abundance of specific microbial communities is significantly correlated with disease severity. For instance, Firmicutes in the gut negatively correlate with PV severity,[18] while *S. aureus* in the skin positively correlates and *S. hominis* negatively correlates with BP severity.[11]

Under disease conditions, compromised skin/mucosal barriers and immunosuppressive therapies (including glucocorticoids, immunosuppressants, and biologics) augment the risk of pathogen proliferation and invasion.[112,113] This scenario may precipitate three outcomes: direct skin/mucosal damage, localized/systemic inflammation which exacerbate disease progression, and localized/systemic infection which elevate mortality risk.[33,34,40,104] Consequently, in disease management, HM modulation has emerged as a promising strategy for optimizing the prognosis of AIBDs.

Potential Therapies Targeting Host Microbiota

Microbiota-targeted treatments, mainly antibiotics, probiotics, and fecal microbial transplantation (FMT), are promising for managing chronic inflammatory skin diseases, such as psoriasis, AD, and AIBDs.

Antibiotics

Tetracyclines (TCNs), including doxycycline, minocycline, and tetracycline, are broad-spectrum antibiotics that inhibit protein synthesis in bacteria.[114] A randomized controlled trial published in The Lancet established that initial doxycycline monotherapy is non-inferior to oral prednisolone for BP treatment in achieving short-term blister control, with superior long-term safety.[115] Minocycline adjuvant therapy enhances BP remission and reduces immunosuppressant requirements, showing potential as monotherapy with minimal side effects (mainly reversible hyperpigmentation) versus conventional systemic treatments.[116,117] Similar benefits extend to pemphigus patients.[118] Substantial evidence supports tetracycline-nicotinamide combination therapy (with or without topical clobetasol) for improving symptoms and survival in both BP and PV.[119–122] Generally, TCNs plus niacinamide is a more effective steroid-sparing strategy than TCNs alone in pemphigus.[122]

Beyond their antibiotic activity, TCNs exhibit potent anti-inflammatory properties, making them effective in treating a range of skin diseases, including AIBDs.[123] Potential mechanisms involve: inhibiting matrix metalloproteinase secretion/activity, suppressing leukocyte chemotaxis, downregulating pro-inflammatory cytokines (including IL-1β, IL-6, TNF-α, and IL-8), inducing caspase-dependent eosinophil apoptosis, reducing eosinophil recruitment, decreasing Th2 chemokines from M2 macrophages, and counteracting staphylococcal exotoxin-mediated survival effects.[114,124,125] Specifically, doxycycline blocks staphylococcal exotoxin-induced T cell proliferation and cytokine/chemokine production, including IL-1β, IL-6, TNF-α, IFN-γ, and monocyte chemotactic protein −1α/1β.[103]

The therapeutic efficacy of erythromycin in BP was initially documented in 1982, showing clinical improvement in two patients, which is likely attributable to its dual antimicrobial and anti-inflammatory properties.[126] Subsequent studies indicate that erythromycin alone or combined with low-dose methylprednisolone is effective in treating BP.[127,128]

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Probiotics

Probiotic supplementation has been widely used in various inflammatory dermatoses, including AD, acne vulgaris, and psoriasis, administered either orally or topically.[129–132] In AIBDs, only one study has evaluated probiotics in MMP, whereas the lack of a non-probiotic group precludes definitive attribution of disease improvement to probiotic use.[133] For

pemphigus and BP, probiotics applications remain unexplored clinically and experimentally. An ongoing clinical trial at the Second Xiangya Hospital of Central South University is assessing oral Bifidobacterium triple viable bacteria in mild-to-moderate PV patients. More studies are expected to be conducted in this realm to further verify its efficacy and safety. Future research should prioritize several critical aspects, including strain selection, administration modes, optimal dosage, and long-term safety profiles.

Fecal Microbiota Transplantation (FMT)

FMT is an emerging therapeutic approach that has demonstrated considerable therapeutic potential for chronic inflammatory skin diseases, including AD, psoriasis, systemic lupus erythematosus, Sjögren's syndrome, and alopecia areata, with significant efficacy and minimal adverse reactions.[134] For example, FMT alleviates AD-induced allergic responses in mice via restoring GM and Th1/Th2 balance, with preliminary clinical efficacy in AD patients.[135,136] According to the latest clinical trial information, a current clinical trial at the China Academy of Medical Sciences Dermatology Hospital is evaluating FMT for mild-to-moderate active BP. Further explorations are required to explore GM-targeted therapies for treating AIBDs by combining appropriate microorganisms or microbial metabolites.

Conclusion and Prospect

This systematic review provides a comprehensive overview of microbiota composition in AIBDs, particularly focusing on pemphigus and BP. Multiple studies have revealed significant alterations in the gut, skin, and OM of AIBDs patients, suggesting microbial dysbiosis may play a crucial role in disease susceptibility, progression, and prognosis. Specifically, the gut-skin axis emerges as a critical pathway linking GM to skin health, with key mediators, such as SCFAs and GABA, influencing immune responses and inflammation. Additionally, CM, particularly *S. aureus*, is implicated in local inflammation and barrier dysfunction, while OM dysbiosis may contribute to both local and systemic immune activation. Whilst we cannot exclude that dysbiosis is a consequence rather than a cause, research data suggest the potential therapeutic applications of microbiota modulation, including antibiotics, probiotics, and FMT, may offer novel strategies for managing AIBDs.

Despite these insights, several limitations hinder generalization and mechanistic understanding. Although the article covers multiple studies, research on the microbiota related to AIBDs remains relatively scarce, particularly concerning the skin and oral microbiota, which may limit the generalizability and reliability of the conclusions. Notably, while the article mentions that microbiota influence diseases through metabolites such as SCFAs and GABA, the precise molecular mechanisms and signaling pathways require further exploration. Furthermore, existing research is predominantly cross-sectional, with rare longitudinal observations of microbiota dynamics (our research group has one such study), making it difficult to determine whether microbiota changes are a cause or a consequence of the disease. Moreover, some studies have small sample sizes and lack diversity analysis across different geographical regions, ethnicities, and age groups, which may affect the representativeness of the results.

Future research is necessary to concentrate on elucidating precise mechanisms underlying microbiota-host interactions and optimizing microbiota-targeted interventions. Longitudinal studies are required to monitor microbiota shifts throughout the disease course, from onset to remission or relapse, to fully grasp the dynamic interactions between microbiota and the diseases. Given the diversity of microbial species and their functional roles, future research should emphasize strain-specific effects and identify potential probiotic candidates for therapeutic use. Additionally, well-designed clinical trials are indispensable for assessing the efficacy and safety of microbiota-targeted treatments, such as probiotics and FMT. Integrating multi-omics approaches, combining microbiome data with genomics, transcriptomics, and metabolomics, could provide a more complete picture of host-microbiota dynamics and identify novel therapeutic targets, ultimately improving patient outcomes.

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Disclosure

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