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REVIEW

The gut-skin axis: Investigating gut microbiota dysbiosis in pemphigus and bullous pemphigoid

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Gut microbiota dysbiosis has been linked with numerous autoimmune disorders and inflammatory skin pathologies. The present study is a narrative review aiming to examine dysregulations in the gut microbiota of patients with pemphigus and bullous pemphigoid, exploring how these alterations may contribute to diseases' development and/or progression. Significant alterations in the composition of intestinal microbiota were identified in patients with pemphigus and bullous pemphigoid: reduction in short-chain fatty acid-producing bacteria: Faecalibacterium prausnitzii, Lachnospiraceae and Coprococcus spp., which are known for their anti-inflammatory effects, and increased abundance of Escherichia coli, Shigella spp., Klebsiella spp., Bacteroides fragilis and Flavonifractor spp., which are recognized for their pro-inflammatory impact. The composition of gut microbiota might influence the pathogenesis of autoimmune bullous diseases. Modified levels of bacteria could become innovative biomarkers for the detection of high-risk individuals, monitoring disease progression and predicting response to treatment. Furthermore, regulating bacterial levels might have therapeutic effects in diminishing inflammation and disease advancement, potentially serving as future therapeutic strategies.

Keywords: pemphigus, bullous pemphigoid, gut microbiota, dysbiosis

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Introduction

Pemphigus and bullous pemphigoid (BP) are autoimmune dermatological diseases, characterized by the formation of blisters and subsequent erosions on the skin and mucous membranes. Lesions are often accompanied by burning, stinging, itching and paresthesia [1, 2]. Both disorders are chronic and recurrent, they primarily affect adult and elderly individuals, and significantly impair their quality of life, especially in severe forms [3, 4].

In pemphigus, the main lesions are flaccid blisters, that develop anywhere on apparently normal skin and mucosae, have thin walls, and are prone to breaking easily, leading to erosions [5]. They appear due to the loss of cohesion between keratinocytes, as autoantibodies attack and destroy desmogleins 1 and 3, which are transmembrane glycoproteins – parts of desmosomes [1]. The underlying pathogenic mechanism, by which these autoantibodies are produced, is not fully understood. Several human leukocyte antigen (HLA) class II alleles confer a genetic susceptibility to the disease: HLA-DRB1*04, HLA-DRB1*14, and HLA-DRB1*08 [6]. In these predisposed individuals, drugs and food, especially with thiol- and phenol-groups, can interact with desmogleins and create neo-epitopes, inducing an autoimmune response. Vaccines and infections, through molecular mimicry, may play a role in pemphigus pathogenesis. Ionizing radiation could modify skin antigen expression, revealing hidden epitopes and triggering autoimmune processes [7].

Clinically, BP is defined by the presence of less fragile and tense bullae, which form on either pre-existing erythematous lesions or apparently intact skin, particularly in flexion areas [5]. As seen in pemphigus, the pathogenesis of BP remains unclear, with similar proposed mechanisms. Predisposing factors (genetic susceptibility, such as HLA-DQB1*03:01, neurological comorbidities, autoimmune diseases, aging process) and triggering factors (drugs, vaccines, viral infections, and physical factors) contribute to or exacerbate the autoantibodies' production. These autoantibodies are directed against glycoproteins BP230 and BP180, which are part of the hemidesmosomes, responsible for maintaining dermo-epidermal adhesion. Their disruption leads to subepidermal blisters [8].

It is noteworthy that BP180 has been found in the human colon epithelium and BP230 – in the gastrointestinal tract of mice. In patients with inflammatory bowel disease (IBD), these self-antigens may be exposed to intestinal T cells, with further recognition of them at the skin level, which could trigger the autoimmune pathogenic process of BP. This hypothesis is also supported by the time gap (years) between the onset of IBD and blistering disorders [9].

The human gastrointestinal microbiota is a complex ecosystem of microorganisms. It plays a central role in maintaining host health and coordinating immune responses, both locally and systemically. Any changes in its diversity, which is called dysbiosis, disrupt the gut homeostasis. Consequently, pathogens and their toxic metabolites cause the activation of immune cells, leading to increased local inflammation and intestinal epithelial dysfunction.

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As a result, not only stimulated immune cells, but also bacterial translocation, with potential cross-reactivity processes, contribute to further dysregulation of the immune system [10]. These mechanisms could be involved in the etiopathogenesis of pemphigus and BP, as recent studies have revealed their implication in several systemic autoimmune disorders, such as IBD, systemic lupus erythematosus and Behçet's disease [11, 12, 13], as well as in numerous inflammatory skin disorders: atopic dermatitis, psoriasis, acne vulgaris [14, 15].

Considering these aspects, our study aims to examine the dysregulation in the gut microbiota of individuals with pemphigus and BP and to explore how these alterations may contribute to the development and progression of the diseases.

Methods

A narrative literature review was conducted using the Pub Med search engine. To fit the scope of the study, the used keywords were: "pemphigus", "bullous pemphigoid", "autoimmune diseases", "gut microbiota", "gut-skin axis", and "dysbiosis" with different combinations of Boolean Operators. The search period was restricted to the last 15 years. The language of publication was restricted to English. To identify relevant studies, snowballing of references was also used.

Interactions between gut microbiota and the immune system in health and autoimmune diseases

The human body has co-evolved with dynamic microorganism communities, collectively known as the microbiome. The microbiota consists primarily of bacteria, which are the most abundant, especially in terms of species diversity, along with archaea, viruses, and fungi. There are several types of microbiotas, including those found in the oral cavity, gut, skin, lungs, and urogenital tract. All of them play an essential role in human homeostasis [16].

The gut microbiota has a unique composition, which is shaped during early life and influenced by external factors, like diet or antibiotic use. However, bacterial genera like *Lactobacillus, Bacillus, Clostridium, Enterococcus* and *Ruminococcus* are the most prevalent in a healthy gut [17]. Normally, inside the intestine, microorganisms and their metabolic products interact, through Toll-like receptors, with gut-associated lymphoid tissues. In this way, they induce the differentiation of immune cells and regulate the balance between helper T cells (Th) and regulatory T cells (Treg) [18]. Furthermore, intestinal microorganisms maintain epithelial and mucin barriers, as they increase the production of tight junctions and related cytoskeletal proteins, and coordinate the formation of mucus layers, through different signaling pathways and gene regulation [19].

Some environmental factors, like diet, lifestyle, stress, drugs and disorders may change the gut microbiome's structure, by reducing its diversity and disturbing taxonomic and metabolite composition. These modifications, especially in hosts with genetic predisposition, alter the interactions between microbiota and the immune system. Results are abnormal mucosal immune responses, which consist of upregulated activity of Th1, Th2 and Th17 cells, downregulated activity of Treg cells and dysregulated antibody-mediated immunity. Moreover, microbes-activated T cells may leave gut-associated lymphoid tissues and disseminate through the bloodstream, initiating a systemic immune response. These processes have been discussed in various autoimmune diseases, like colitis, multiple sclerosis and systemic lupus erythematosus [18, 19, 20]. Additionally, intestinal inflammation compromises epithelial and mucin barriers, so microbes and their metabolites, such as lipopolysaccharides, can translocate from the gut into the circulation, inducing systemic inflammation [18, 19]. They may also reach other tissues or organs where, due to cross-reactivity, they can trigger autoimmune responses, as seen in Sjögren's syndrome [21] and rheumatic diseases (rheumatoid arthritis, ankylosing spondylitis, and Crohn's disease) [22].

The gut microbiota influences skin homeostasis through different mechanisms. Intestinal microbes generate metabolic products, neurotransmitters and hormones, which can reach the skin via systemic circulation. Conversely, the skin produces various compounds, like vitamin D, that could potentially affect the gut, establishing a bidirectional connection between them, known as the gut-skin axis. As previously mentioned, the intestinal microbiota can modulate immune responses in distant organs, including the skin, by affecting immune cells, particularly Th1, Th2, Th17, and Treg cells. Also, this influence may occur more directly, through the translocation of intestinal bacteria and their metabolites into the bloodstream, which subsequently accumulate at the skin level [23]. Supporting this hypothesis, studies have indicated the presence of genetic material from intestinal bacteria in the blood of psoriatic patients [24].

As dysregulation within the gut-skin axis is involved in several inflammatory dermatological disorders, like atopic dermatitis, psoriasis, rosacea and acne vulgaris [14, 15], the mechanisms discussed before could be also relevant in the case of pemphigus and BP. Studies revealed that an imbalance between Th2 and Th1 cells, an increased population of Th17 and a decreased population of Treg cells play a crucial role in the etiopathogenesis of both diseases. Th2 cells and interleukin (IL)-4 stimulate B cell proliferation and autoantibody production. Th17 cells infiltrate the skin, produce IL-17, and consequently activate neutrophils, intensifying inflammatory reactions and tissue damage. Reduced levels of Treg lead to abnormal activation of autoreactive Th cells, with subsequent autoantibody production [25].

Oxidative stress, caused by elevated levels of reactive oxygen species (ROS), has also been suggested as a contributing pathogenic factor for autoimmune skin diseases. ROS stimulate the transcription factors for different pro-inflammatory cytokines, enhance cell death and may trigger

an autoimmune response, with autoantibody production [26]. It has been shown that ROS generation in erythrocytes and neutrophils was significantly higher in patients with active vitiligo compared to healthy controls. Moreover, increased production of circulatory pro-inflammatory cytokines was associated with elevated levels of ROS and decreased levels of antioxidants [27]. The exact relationship between oxidative stress, the gut microbiome, and the pathogenesis of inflammatory skin diseases remains unclear. Complex interactions within the gut-skin axis may influence the balance of ROS, both locally and systemically, with further activation of the inflammatory cascade and contribution to disease development [28].

Hence, considering the significant impact of intestinal microbiota on the host immune system and the presumed mechanisms involved in the etiopathogenesis of pemphigus and BP, we will explore how specific gut microbes, their metabolites and their functions may contribute to local immune alterations. As immune dysregulation at the intestinal level could lead to systemic inflammatory consequences, these changes may potentially explain, at least partially, the occurrence and progression of both diseases.

Gut microbiota dysbiosis in pemphigus and BP

Decrease in *Faecalibacterium prausnitzii*

In a study conducted by Liu at al. [29], the gut microbiota was compared between 66 patients with BP and 66 age-, sex-, and study center-matched controls with non-inflammatory skin disorders, utilizing 16S rRNA gene and shotgun sequencing data. Findings indicated a reduction in alpha-diversity and significant alterations in the composition of the intestinal microbiota in BP patients. Moreover, they detected some modifications associated with BP, such as decreased levels of *Faecalibacterium prausnitzii* (*F. prausnitzii*), which is a member of the Firmicutes phylum and a prevalent species in the normal gut microbiota. The same significant reduction in Firmicutes was discovered in fecal samples and correlated with disease activity in 43 pemphigus patients, compared to 26 age-, sex- and body mass index-matched healthy controls, using metagenomic sequencing and liquid chromatography-mass spectrometry metabolome sequencing [30].

F. prausnitzii, a promising candidate for next-generation probiotics development, is a Gram-positive, strict anaerobe, commensal bacterium [31]. It produces butyrate, a short-chain fatty acid (SCFA), which represents a primary source of energy for colonocytes. SCFAs enhance the epithelial barrier function, reduce the accumulation of potentially toxic metabolites, such as D-lactate and play a crucial role in regulating mucosal immunity, as they have anti-inflammatory effects. They suppress the signaling of interferon-gamma (IFN-γ), inhibit the activation of nuclear factor kappa-light-chain-enhancer of activated B cells and increase the expression of peroxisome proliferator-activated receptor gamma. Moreover, SCFAs modulate the development of intestinal Tregs, improving their function, and preventing the occurrence of inflammatory disorders, such as allergies and colitis [32, 33].

In vitro, *F. prausnitzii* exhibited several effects on peripheral blood mononuclear cells, demonstrating its ability to promote a tolerogenic cytokine environment. This included reduced production of pro-inflammatory IL-12 and IFN-γ, and increased release of anti-inflammatory IL-10 [34]. Furthermore, the *F. prausnitzii* supernatant diminished inflammation in dextran sodium sulphate-induced colitis in murine models, due to metabolites that improved intestinal barrier function and influenced paracellular permeability [35].

The notably diminished abundance of *F. prausnitzii* in gut microbiota was also detected in other inflammatory skin disorders. In psoriatic patients, the level of this bacterium was significantly lower than in healthy controls, but similar to individuals with IBD. Additionally, the analyses showed the most pronounced reduction in *F. prausnitzii* in patients with concomitant psoriasis and IBD [36]. Similar alterations were observed in patients with atopic dermatitis, alongside an association between a higher relative abundance of this microorganism and reduced disease severity [37].

Based on these findings, the decrease of *F. prausnitzii* in the gut microbiota may contribute to local immune dysregulation and potentially lead to systemic inflammatory consequences. This could have implications for the onset and/or progression of autoimmune bullous diseases, especially in individuals with genetic susceptibility. Thus, *F. prausnitzii* may become an important biomarker for the detection, monitoring, and even treatment of these diseases, as a live biotherapeutic product.

Decrease in *Lachnospiracea and Coprococcus* spp.

Huang et al. [38] investigated fecal bacterial composition using 16S rRNA gene sequencing and assessed plasma levels of 20 inflammatory cytokines, using the Luminex screening system, in 18 individuals with pemphigus vulgaris, comparing them to 14 age- and gender-matched healthy controls. They noticed a decrease in the abundance of SCFAs-producing bacteria, such as *Lachnospiracea incertae sedis* and *Coprococcus* spp., in the gut of pemphigus patients. Lower levels of bacteria from the family Lachnospiraceae were also identified in pemphigus individuals [30]. Low et al. [39] analyzed fecal samples from 49 patients with ocular mucous membrane pemphigoid and 40 healthy controls, using 16S rRNA gene sequencing, and concluded that bacteria from the family Lachnospiraceae and genus *Coprococcus* were less prevalent in individuals affected by the disorder compared to healthy controls. In a study conducted by Hu et al. [40], fecal samples from 24 patients with BP onset, 24 patients under BP remission, and 24 healthy controls were evaluated using 16S rRNA sequencing. Results highlighted that bacteria from the family Lachnospiraceae had higher levels in both healthy controls and the remission group compared to patients with BP onset.

Similar findings were observed in other inflammatory skin conditions. In the case of chronic spontaneous urticaria, patients who responded to second-generation oral antihistamines had higher levels of bacteria from the family Lachnospiraceae compared to those patients that are refractory to treatment, establishing Lachnospiraceae as a predictive marker for antihistamine effectiveness in this condition [41]. In patients with atopic diseases, the severity of eczema showed a negative correlation with gut microbiota diversity and the abundance of butyrate-producing bacteria, especially *Coprococcus eutactus*. This suggests their potential involvement in diminishing symptoms of atopic eczema [42]. The beneficial effects of these bacteria could be attributed to the anti-inflammatory properties of butyrate, which is the end product of their metabolism [43]. However, other mechanisms may also be involved, requiring further research.

Increase in *Flavonifractor* spp.

In contrast with decreased SCFAs-producing bacteria in the gut microbiota, patients with BP have demonstrated elevated levels of *Flavonifractor* spp. (formerly known as *Eubacterium* spp.) [29]. These bacteria cleave quercetin, a flavonoid known not only for its antioxidant properties, as it acts like a ROS scavenger, but also for its anti-inflammatory effects, as it reduces oxidative stress and inhibits cytokine production induced by lipopolysaccharide [44]. The same increased abundance in *Flavonifractor* spp. was found in patients with pemphigus vulgaris. Additionally, a positive correlation was observed between *Flavonifractor* spp. and systemic levels of inflammatory mediators (IL-1β, IL-6, IL-8, IL-7, IL-21, C5a), providing evidence for the pro-inflammatory effects of this bacterium via the metabolism of quercetin [38].

Therefore, considering these aspects, elevated levels of *Flavonifractor spp*. might disrupt intestinal immune responses, resulting in systemic inflammatory consequences. These alterations, particularly in genetically predisposed individuals, could potentially contribute to the development or exacerbation of pemphigus and BP.

Increase in *Proteobacteria* and *Bacteroides fragilis*

Wang et al. [45] compared the fecal bacterial composition of 60 patients with pemphigus vulgaris and 19 matched healthy family members, using metagenomic shotgun sequencing and metabolomics analysis. Their findings revealed a higher abundance of *Escherichia coli (E. coli)* in patients with pemphigus vulgaris compared to healthy controls. Moreover, a notable reduction in E. coli was observed after glucocorticoid treatment, which suggests a possible association between this bacterium and pemphigus onset.

Another study showed that patients with pemphigus vulgaris had a pronounced enhancement of the Enterobacteriaceae family, specifically the *Escherichia-Shigella* genus [38]. Besides a higher level of *E. coli*, an increased relative abundance of *Bacteroides fragilis* and *Klebsiella pneumoniae* has also been reported. Their levels were positively correlated with pemphigus disease activity [30]. Furthermore, Enterobacteriaceae were found to be more abundant in patients with BP onset, compared to the remission group and healthy controls [40].

The expansion of Proteobacteria family in gut microbiota is a hallmark of epithelial dysfunction and has been detected in multiple diseases [46]. Its member, *E. coli*, as a Gram-negative bacterium, contains a complex glycolipid in its membrane, called lipopolysaccharide, which is essential for bacterial virulence. Lipopolysaccharides can trigger a strong inflammatory reaction through Toll-like receptor 4 signaling, with a further release of numerous pro-inflammatory cytokines (IL1β, IL6, IL8, tumor necrosis factor alpha (TNF-α), transforming growth factor beta, etc.), potentially causing impairment of the intestinal barrier. The compromised gut barrier allows pathogens and toxins to cross into the lumen and enter the systemic circulation. Thus, through different mechanisms, including cross-reactivity, they could initiate and contribute to the development of autoimmune disorders, like type 1 diabetes, systemic lupus erythematosus and multiple sclerosis [20, 47].

In Sjögren's syndrome, the activation of Ro60-reactive T cells by *E. coli* expressing von Willebrand factor A underscores the role of Proteobacteria in triggering autoimmune responses through a mimicry mechanism [21]. The same mechanism might link the subclinical bowel infections with *Klebsiella* spp. to the etiopathogenesis of ankylosing spondylitis and Crohn's disease [22]. Since both pemphigus and BP are autoimmune disorders, this etiopathogenetic process should be considered and perhaps investigated in detail in the future.

The high abundance of *E. coli* in gut microbiota has been also associated with inflammatory dermatological diseases, such as atopic dermatitis. Studies have shown that *E. coli* was more prevalent in infants with atopic dermatitis compared to healthy controls. Additionally, levels of *E. coli* correlated with disease severity [37]. The same notable increase of *E. coli* in intestinal microbiota has been demonstrated in patients with psoriasis. Moreover, individuals who had both psoriasis and IBD exhibited the most significant increase in *E. coli* abundance [36].

Taken together, these findings suggest a possible contribution of elevated levels of Proteobacteria, specifically *E. coli, Shigella* spp., *Klebsiella* spp., and *Bacteroides fragilis* in the pathogenesis of autoimmune bullous diseases. Consequently, regulating their expansion could have therapeutic effects in diminishing inflammation and disease advancement (Figure 1).

Influence of antibiotics, prebiotics and probiotics on immune-mediated skin pathologies

BLISTER trial showed that initiating BP patients on doxycycline (200 mg/day) is as effective as standard oral prednisolone therapy (0.5 mg/kg/day) for short-term blister

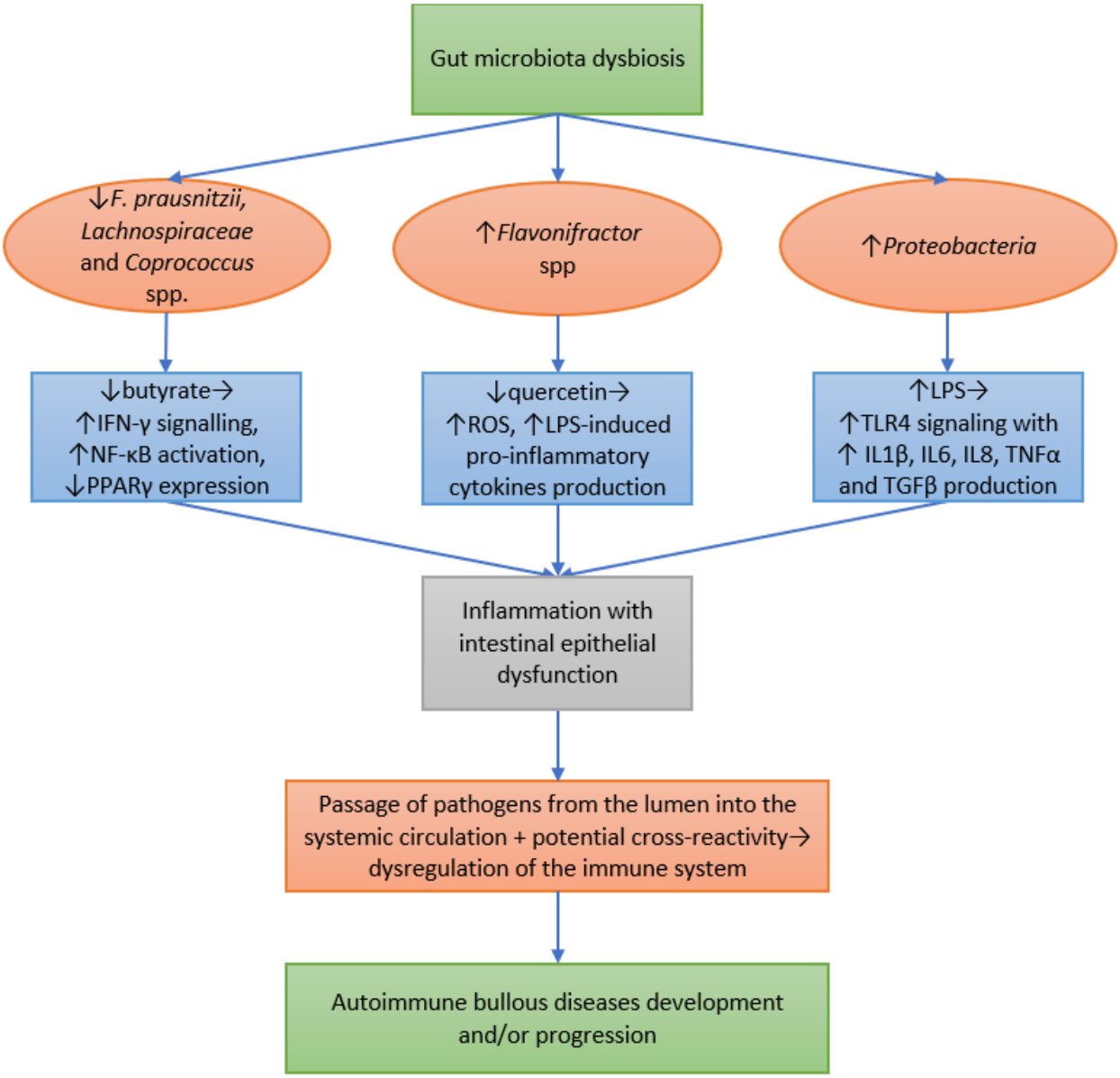

Fig. 1. Gut microbiota dysbiosis in pemphigus and bullous pemphigoid: key bacteria and potentially involved mechanisms. *F. prausnitzii: Faecalibacterium prausnitzii*; IFN-γ: interferon gamma; IL: interleukin; LPS: lipopolysaccharide; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PPARγ: peroxisome proliferator-activated receptor gamma; ROS: reactive oxygen species; TGFβ: transforming growth factor beta; TLR4: toll-like receptor 4; TNF-α: tumor necrosis factor alpha.

management and significantly long-term safer. The results of the randomized controlled trial revealed that individuals experiencing mild to moderate BP should undergo treatment depending on the safety and efficacy of the medications, as well as patient preference. Neither approach emerges as definitively preferred [48, 49]. In addition to the immunomodulatory and anti-inflammatory effects of tetracyclines, their influence on intestinal microbiota could serve as a possible mechanism contributing to the therapeutic effect observed in BP patients [50]. This underscores the potential therapeutic role of microbiota modulation by antibiotics in the treatment of pemphigus and BP.

Prebiotics and probiotics have shown promise in alleviating skin lesions by modulating the gut microbiota, presenting a potential therapeutic strategy for skin diseases. Prebiotics are non-digestible carbohydrates that can be utilized by host microorganisms, providing health benefits. They are fermented into SCFAs, which are known to have local and systemic anti-inflammatory effects. Probiotics instead are living bacteria that, ingested in adequate amounts, prevent pathogenic microorganisms from colonizing the gut, hinder their epithelial and mucosal adherence, restore the intestinal barrier, generate metabolites with anti-inflammatory properties, and influence the reactivity of the immune system [33]. Additionally, probiotics can also stimulate the intrinsic gut proliferation of SCFAs-producing bacteria [51].

Groeger et al. [52] showed that oral supplementation with *Bifidobacterium infantis 35624,* in individuals with psoriasis, notably reduced the plasma concentrations of TNF-α, IL-6, and C-reactive protein, which are important indicators of inflammation. Psoriatic patients who received local anti-psoriatic therapy along with oral probiotics and prebiotics demonstrated better outcomes in terms of dis-

ease activity, as measured by the Psoriasis Area and Severity Index, Dermatology Life Quality Index, inflammatory markers, and skin thickness, compared to those who did not receive supplementation [53]. In adult patients with atopic dermatitis, the administration of probiotics, primarily *Lactobacillus* and *Bifidobacterium* strains, resulted in a significant reduction in Scoring Atopic Dermatitis, accompanied by an improvement in their quality of life [54]. Cesaroni et al. [55] monitored patients with pemphigoid lesions and psoriasis who received an oral probiotic solution, containing four varieties of *Lactobacilli*. The authors assessed skin lesions at 30, 60, and 90 days of treatment and observed that probiotics could restore and heal the skin through their immunomodulatory actions in the gut. Furthermore, innovative methods of fecal transplantation have been presented as promising therapeutic strategies for patients with psoriasis and atopic dermatitis [56, 57].

Considering the alterations of gut microbiota, detected in patients with pemphigus and BP and the beneficial effects of prebiotics, probiotics and fecal transplantation in other immune-mediated dermatological disorders, further studies are required to elucidate the therapeutic potential of modulating the intestinal microbiota in autoimmune bullous diseases.

Experimental models for studying microbiota in pemphigus and BP

In the studies previously mentioned, the fecal microbiota of patients with pemphigus and BP was examined using various methods including 16S rRNA gene sequencing, shotgun metagenomic sequencing, and liquid chromatography-mass spectrometry metabolome analysis. The results were then compared to those of matched healthy individuals [29,30,38,39,41,45].

There are various mouse models of pemphigus, including those induced by antibody transfer, lymphocyte transfer, and immunization. Similarly, there are immunization-induced mouse models for BP [58, 59]. To our knowledge, these models have not yet been utilized to investigate the interplay between intestinal microbiota and the pathogenesis of pemphigus and BP. This presents a promising perspective for future research.

Conclusion

Patients diagnosed with pemphigus and BP demonstrate significant alterations in their gut microbiota when compared with healthy individuals. Among these changes, is particularly noteworthy the reduction in SCFAs-producing bacteria, specifically *F. prausnitzii, Lachnospiraceae* and *Coprococcus* spp., which are known for their anti-inflammatory effects. Additionally, there is an increased abundance of Proteobacteria, notably *E. coli*, and *Flavonifractor*, which are recognized for their pro-inflammatory influences. These modifications could potentially play a role in the dysregulation of the immune system, as seen in autoimmune bullous diseases, thereby contributing to the disorders' development and/or progression. Bacteria mentioned before could become innovative biomarkers for the detection of high-risk individuals, monitoring disease progression, predicting response to treatment, and potentially serving as components for future therapeutic strategies, used as live biotherapeutic products. Further phenotyping studies should explore the role of gut microbiome changes in the pathogenesis of autoimmune bullous diseases and elucidate their potential therapeutic applications.

Authors' contribution

AN (Conceptualization; Formal Analysis; Investigation; Methodology; Writing – original draft);
CC (Conceptualization; Formal Analysis; Methodology; Supervision; Writing – review & editing);
CA (Conceptualization; Formal Analysis; Methodology; Supervision; Writing – review & editing).

Conflict of interest

None to declare.

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