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The microbiome and immunodeficiencies: Lessons from rare diseases

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ABSTRACT

Primary immunodeficiencies (PIDs) are inherited disorders of the immune system, associated with a considerable increase in susceptibility to infections. PIDs can also predispose to malignancy, inflammation and autoimmunity. There is increasing awareness that some aspects of the immune dysregulation in PIDs may be linked to intestinal microbiota. Indeed, the gut microbiota and its metabolites have been shown to influence immune functions and immune homeostasis both locally and systemically. Recent studies have indicated that genetic defects causing PIDs lead to perturbations in the conventional mechanisms underlying homeostasis in the gut, resulting in poor immune surveillance at the intestinal barrier, which associates with altered intestinal permeability and bacterial translocation. Consistently, a substantial proportion of PID patients presents with clinically challenging IBD-like pathology. Here, we describe the current body of literature reporting on dysbiosis of the gut microbiota in different PIDs and how this can be either the result or cause of immune dysregulation. Further, we report how infections in PIDs enhance pathobionts colonization and speculate how, in turn, pathobionts may be responsible for increased disease susceptibility and secondary infections in these patients. The potential relationship between the microbial composition in the intestine and other sites, such as the oral cavity and skin, is also highlighted. Finally, we provide evidence, in preclinical models of PIDs, for the efficacy of microbiota manipulation to ameliorate disease complications, and suggest that the potential use of dietary intervention to correct dysbiotic flora in PID patients may hold promise.

1. Introduction

Primary immunodeficiencies (PIDs) are a heterogeneous group of over 330 disorders that result from defects in immune system development and/or function [1]. PIDs are broadly classified as disorders of adaptive (i.e., T-cell, B-cell or combined immunodeficiencies) or innate immunity (i.e., phagocyte and complement disorders), all of which lead to an aberrantly functioning immune system and predispose to recurrent, chronic, atypical, or severe infections.

In addition, several PIDs are associated with presumed non-infectious complications such as granulomas, lymphoproliferative disease, malignancy and/or autoimmunity, contributing significantly to morbidity and mortality [2]. These complications suggest an underlying state of immune dysregulation that may result from chronic systemic activation. In other words, persistent low-grade chronic inflammation may drive immune pathways involved in autoimmunity [3]. Studies in mice and humans with autoimmune diseases have described genotype-driven alterations in the intestinal microbiome which may play a significant role in disease onset and/or progression [4]. It has long been appreciated that the immune system can shape the composition of the microbiota, which in turn can influence the development and function of the innate and adaptive immune systems as they relate to immune homeostasis and host-microbe coexistence [5]. In the setting of defects in immune function, impaired immunosurveillance at the level of the intestinal mucosa could result in dysbiosis, which leads to increased permeability and local inflammation. The clinical corollary to this is that a substantial proportion of patients with PIDs exhibits gastrointestinal complications and inflammatory bowel disease (IBD)-like pathology (Fig. 1) [6–8]. The impairment of mucosal barrier function and the resulting absorption of microbial antigens into the systemic compartment are considered to be the major underlying causes of the continuous activation of $CD4^+$ and $CD8^+$ T cells in autoimmune

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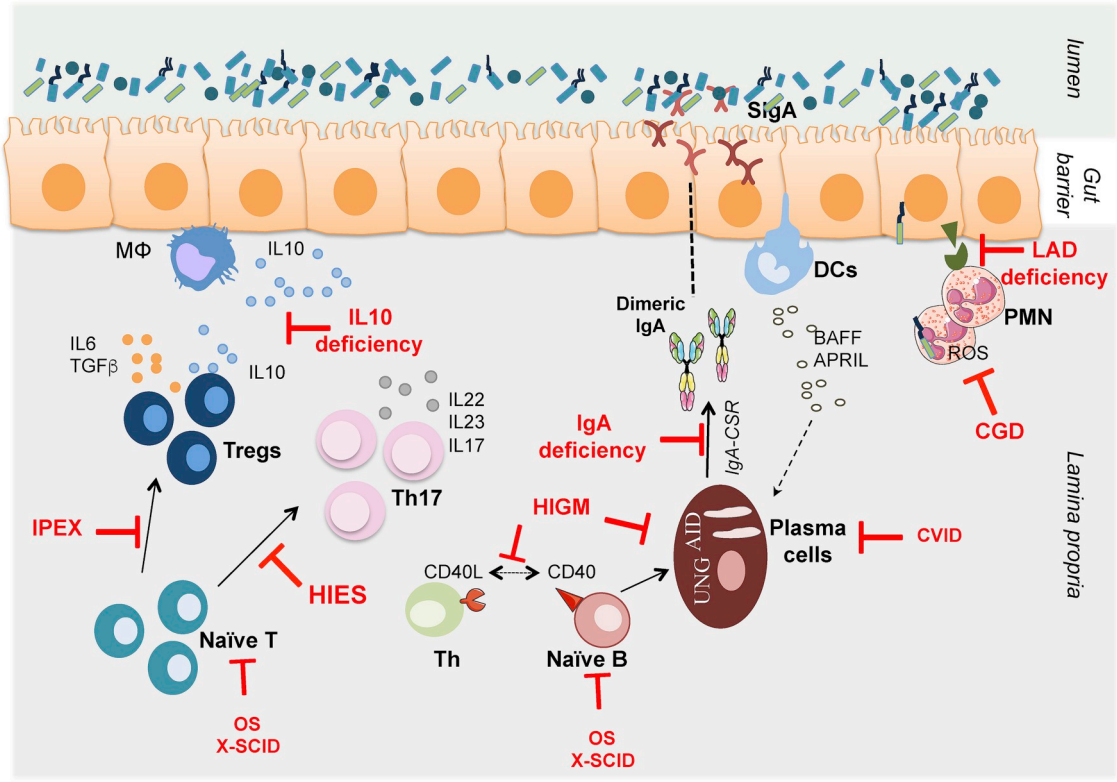

Fig. 1. Primary immune deficiency disorders affecting intestinal homeostasis. Intestinal environmental factors and host immunity are critical to regulate gut homeostasis. Defects in either adaptive or innate immune pathways result in aberrant inflammatory response, damage of gastrointestinal tract and increased risk to develop inflammatory and autoimmune disorders. These conditions are found in different PIDs. SCID, severe combined immune deficiency; OS, omenn syndrome; HIES, hyper-IgE syndrome; IPEX, X-linked immune dysregulation, polyendocrinopathy, enteropathy syndrome; HIGM, hyper-IgM syndrome; CVID, common variable immune-deficiency, SIgAD, selective-IgA deficiency; LAD, leukocyte adhesion deficiency; CGD, chronic granulomatous disease.

disease and HIV-1 infection [4,9]. A potential role for microbial translocation in PID immunopathology is increasingly appreciated.

We will review the current evidence supporting a role for the intestinal microbiome in the pathogenesis of PIDs. Particularly, we will focus on the mechanisms by which PIDs cause shifts in the human gut microbiota composition and how dysbiosis can cause immune dysregulation. The possible contribution of the microbial communities in other niches, such as the oral cavity and skin, will also be highlighted. Finally, we will provide data on the effect of microbiota manipulation in animal models of PIDs and discuss how it can translate into a therapeutic option for human patients.

1.1. Conventional mechanisms of intestinal homeostasis

The digestive tract is in direct contact with foreign antigens and microorganisms. The ability of the immune system to maintain tolerance to non-pathogenic intestinal antigens, such as food and molecular components of the microbial flora, while remaining capable of responding to infection with pathogens is essential for tissue homeostasis. Failure of such a harmonized balance may result in different pathological conditions in the intestine and systemic diseases [10]. To minimize such pathological conditions, the intestinal tract has evolved mechanisms to regulate microbiota through different strategies.

The intestinal epithelium, a single cell layer kept together by tight junctions that regulate paracellular permeability, mediates the physical segregation of the microbiota in the intestinal lumen. In addition, the epithelium is covered by mucus layers of different thickness and mucin (MUCs) composition along the intestinal tract, which help retaining commensal flora in the intestine by providing ample binding sites, while minimizing the attachment of pathogenic bacteria [11]. Intestinal epithelial cells also secrete antimicrobial peptides (AMPs) that protect intestinal crypts from bacterial overgrowth and support the integrity of the epithelium. Their impaired production is associated with intestinal and systemic inflammation [12,13]. The anti-inflammatory activity of these AMPs is supported by IgAs, produced by B cells and plasma cells that reside in the Peyer's patches and intestinal lamina propria. Paradoxically, the production of these molecules, allowing symbiotic relationship with the microbiota, is regulated in the gut by the same immune receptors (pattern recognition receptors, PRRs) and environmental sensors that initiate inflammatory reactions in response to invading pathogens; the outcome of signal recognition depends on the cooperation with other receptors and the type of environment conditioning by cytokines and other factors [14]. Mutations in the NLRP protein Nod2, which are strongly associated to Crohn's disease, were found to negatively affect the production of a subgroup of intestinal anti-microbial peptides known as cryptidins [12]. RegIII lectins are produced by Paneth cells in response to MyD88-dependent recognition of gut microbial patterns [15]. The action of AMPs and IgAs is supplemented by MUCs which, when activated by NLRP6, protect mice from inflammation [16]. PRR-dependent Muc2 production also induces expression of anti-inflammatory genes in dendritic cells [17]. Similarly, the involvement of TLRs in IgA-dependent sculpting of microbiota composition has been demonstrated in studies of T follicular helper cells, which upon TLR activation promote class switch recombination of B cells towards production of IgA [18].

In addition to maintaining a functional barrier, IECs contribute to tissue homeostasis by curbing unwanted response to common bacterial antigens. Despite its ability to induce potent systemic inflammatory responses, lipopolysaccaride (LPS) fails to induce inflammation in the intestine when administered parenterally. In vitro studies attribute lack of response to LPS in IEC lines to their minimal expression of toll-like receptors (TLRs) [19]. Furthermore, mRNA for CD14, a glycoprotein

that functions with TLR-4 as a high affinity receptor for LPS, is not detected in some IEC lines [20]. In the gut epithelium, down-regulation of TLRs occurs on the apical membrane compared to the basolateral side [21,22]. On the contrary, the epithelial alkaline phosphatase, the enzyme that dephosphorylates bacterial LPS rendering this molecule tolerogenic due to inability to stimulate TLR9, is concentrated closely to the apical membrane, thus providing a mechanism by which IECs can detect and respond to invasive bacteria while remaining tolerant to luminal flora on their apical surface [23]. Furthermore, studies indicate that, unlike abrupt activation, persistent stimulations of the basolateral TLRs result in receptor internalization and tolerance induction [24,25]. Thus, PRRs tend to induce inflammatory responses in reaction to rapid alterations in the dynamics of receptor/ligand interactions (i.e. newly arrived microbial communities); in contrast, chronically acquired microbial communities, such as those acquired soon after birth, fail to induce these inflammatory responses and can become established and persist [26].

In addition to IECs, stromal cells and professional antigen presenting cells (APCs) contribute to mucosal tolerance by influencing T cell differentiation. Stromal cells in the murine *lamina propria* constitutively express cyclooxygenase (COX-2) and produce abundant level of prostaglandin E2 (PGE_2), with immunoregulatory function [27]. Human intestinal macrophages lack CD14, secrete modest quantities of pro-inflammatory cytokines and, compared with monocytes from peripheral blood, do not support proliferation of peripheral blood T cells, likely due to the diminished expression of costimulatory molecules [28]. In addition, *lamina propria* macrophages do not express CD89, the receptor for IgA (FcRa), thereby reducing IgA-enhanced phagocytosis [29]. Although low level of CD89 is expressed by dendritic cells (DCs), these cells efficiently bind secretory IgA via the carbohydrate-binding mannose receptor, without induction of cell maturation [30]. Similarly to IECs, intestinal APCs are hyporesponsive to TLR-stimulation, at the steady state. Both the intestinal epithelium and immune cells can explore several options to down-regulate TLR-dependent stimulation, including decrease of TLRs expression, release of soluble immune receptors such as TLR2, TLR4 and ST2, and up-regulation of intracellular inhibitors of TLR signaling, including MyD88s (a splice variant of myeloid differentiation factor 88), Toll-interacting protein (Tollip), TNF-related apoptosis-inducing ligand receptor (TRAIL-R), selective androgen receptor modulator (SARM), and others [31]. Decoy receptor such as single Ig IL-1-related receptor (SIGIRR), highly expressed by immature intestinal APCs, also contributes to colonic epithelial homeostasis by inhibiting TLR-induced gut inflammation [32].

The high number of Treg cells in the gut provides an important mechanism for the maintenance of tolerance to both commensals and food antigens. However, although the two processes share some features, they are fundamentally different. Indeed, tolerance to microbes is largely limited to the gut whereas tolerance to food proteins induced through the small intestine influences both local and systemic immune responses [33], and hence could play a key role in the maintenance of peripheral immune homeostasis [34]. The gut-draining mesenteric lymph nodes (mLNs) play a critical role in the induction of antigen-specific Treg cells (inducible Tregs, iTregs) [35]. Treg cell induction in the mLNs involves the cooperative action of gut-derived CD103 + DCs and stromal cells that metabolize dietary vitamin A to RA, which is required also for imprinting of gut-homing receptors on primed T cells [36–38]. Induced-Tregs that leave the mLN and home to the small intestine undergo secondary expansion activated by IL-10-secreting $CX3CR^{high}$ myeloid cells and resident macrophages [39]. Some secondarily expanded Tregs can possibly leave the *lamina propria* and enter the circulation, thereby contributing to expanding local tolerance to orally administered antigens systemically. Regular stimulation by commensal bacteria contributes maintaining Tregs and mucosal IgA in the gut [40,41]. In addition, innate lymphoid cells (ILCs), plays a critical role in integrating signals from the commensal microbiota to maintain homeostasis at epithelial barriers and guide adaptive immunity [42].

Thus, the intestinal microbiota itself has a crucial role in the maintenance of the intestinal microenvironment promoting tolerance. Commensal flora contributes to intestinal tolerance by limiting intestinal inflammation directly, by restraining transcription of inflammatory mediators such as cytokines, chemokines and adhesion proteins [43], and indirectly, by minimizing bacterial antigen immunogenicity [44]. Colonization of the intestine is central to normal immune development and function as well as for induction of tolerance. Consistently, intestinal tolerance cannot be induced in germ-free animals, whilst presence of LPS in the gut is an important determinant of natural tolerance induction [45,46]. Accordingly, more recent studies have shown that early colonization with a protective microbiota can reduce the risk of autoimmunity development in genetically susceptible animals, as well as protect mice from allergies [47,48]. This evidence reconciles the original idea proposed in the “hygene hypothesis”, according to which there is an association between changes in microbial exposure in early childhood and increasing incidence of allergic and autoimmune diseases [49]. In this context, an overly hygienic lifestyle may induce aberrant colonization of the neonatal intestine, excluding microbes important for immune education [50–52]. The distinction between beneficial and harmful microbial communities and their mode of action are starting to be unveiled; *Vatanen* et al. [53] proposed that structural differences in LPS molecules from different species of bacteria have different immunostimulatory profiles that could impact long-term immunosuppressive mechanisms. Indigenous intestinal bacteria also control enteric colonization by potential pathogens. This phenomenon, known as “colonization resistance” and involving direct interaction among microorganisms, secretion of molecular mediators and competition for the same biological niches, allows maintaining a stable intestinal ecology that benefits themselves and the host [54–56]. Defaults in several of these conventional mechanisms of intestinal homeostasis are reported in patients with PID, as consequence of their genetic defects.

2. Microbiota in complex defects of T and B cell selection and activation

2.1. Common variable immunodeficiency (CVID)

Common variable immunodeficiency (CVID) is a heterogeneous group of disorders characterized by hypogammaglobulinemia associated with B cell, T cell, and dendritic cell defects [57]. Genetic mutations associated with CVID have been identified in only 15–20% of cases. In particular, mutations in the *TNFRSF13B*, *ICOS*, *CD19*, *CD20* and *CD81* genes have been described [58]. These patients suffer from increased susceptibility to bacterial infections, which mainly involve the mucus membranes, and are predominantly caused by *Streptococcus pneumoniae, Klebsiella pneumoniae* and *Haemophilus influenzae.* In addition to immunodeficiency, more than half of patients with CVID develop noninfectious complications such as malignancies, autoimmunity, and lymphoproliferative and granulomatous disease, which often affect the gastrointestinal tract [59].

The main gastrointestinal manifestation of CVID is transient or persistent diarrhea, found in 21%–57% of subjects [60]. When a cause is identified, *Giardia lamblia*, *Cryptosporidium parvum*, *cytomegalovirus*, *Salmonella species*, *Clostridium difficile*, and *Campylobacter jejuni* are the most common pathogens. *H. pylori* infection has been associated with gastritis. Aside from intestinal bacterial and parasitic infections, IBD remains a significant problem in 19%–32% of patients [6]. On biopsy, the gastrointestinal mucosa contains excess intraepithelial lymphocytes, villous blunting, granulomas, crypt distortion, the characteristic lack of plasma cells and nodular lymphoid hyperplasia, obviously reflecting a response to gut antigens [61,62].

Another common feature is villous flattening in the small intestine suggesting celiac sprue. The significant loss of essential nutrients might

lead to often irreversible bone and neurological defects.

2.1.1. Microbiota and immune dysregulation in CVID

Recent studies suggest that the immune dysregulation underlying the complications observed in CVID may be the consequence of altered microbiota composition and increased microbial translocation [59]. IgA against commensals is induced in the Peyer's patches (PP), where live bacteria transported by DC are presented to B and T cells [63]. In addition, secretory IgA has the ability to selectively adhere to M cells in the intestinal PP and to stimulate the subsequent uptake of IgA-bound antigens for delivery to DCs, thereby promoting a positive feedback loop [64,65].

Therefore, IgA has a fundamental role in limiting the pro-inflammatory response to the bacteria it coats, in the maintenance of intestinal mucosal barrier integrity, as well as in shaping the composition of the intestinal microbiota [66,67]. In fact, mice lacking IgA have significantly lower intestinal microbial diversity than wild-type littermates [68]. Moreover, mucosal IgA, but not IgM, is critical in preventing the attachment of segmented filamentous bacteria (SFB) to the gut epithelium, as well as the resulting immune activation [69]. Likewise, IgM cannot deliver Ags to PP because it cannot bind to M cells [70].

In CVID, IgA deficiency is strongly correlated with increased morbidity from inflammation [71]. Therapy with immunoglobulin substitution (IVIG), restoring IgG but not IgM or IgA levels, resolves the specific immune deficiency without any improvement in immune dysregulation [60]. Gut epithelial damage in CVID patients may be affected by IgA deficiency, which may allow mucus invasion and epithelial infection.

Jorgensen et al. [72] performed the first cross-sectional study of the intestinal microbiota in CVID patients (n = 44) compared with healthy controls (n = 263) and patients with Crohn disease (CD) or ulcerative colitis (UC) (n = 45), as disease controls. Stool samples were excluded from CVID patients under antibiotic or immunosuppressive treatments, and users of self-reported special diets. Microbial richness in CVID patients, defined by the CHAO1 diversity index, was markedly lower compared to controls. Interestingly, it did not differ from that in IBD patients, though the two cohorts retained distinct taxonomic profiles. CVID patients exhibiting immune dysregulation not limited to the gastrointestinal tract had more gut dysbiosis than patients with infections only. Moreover, patients with severe IgA-deficiency had significantly reduced alpha diversity indices compared to patients retaining low or normal IgA levels, whereas no correlation was detected for IgG or IgM levels. Four bacterial taxa were more abundant in CVID than in healthy donors: *Clostridia* (*Lachnospiraceae Dorea* and *Lachnospiraceae Roseburia* genera*), Bacilli* and *Gammaproteobacteria.* On the contrary, bacteria belonging to *Firmicutes* (*Christensenellaceae* family and *Lachnospiraceae Blautia* genus), *Actinobacteria* (e.g. *Bifidobacteriaceae* family), and *Deltaproteobacteria* (*Desulfovibrionales* genus) classes were found to be drastically decreased in CVID [72] (see Table 1). The reduced *Firmicutes* and *Actinobacteria* diversities were also found in an independent study with a smaller group of CVID patients [73]. The presence of bacteria belonging to the *Blautia* genus has been linked to protection from lethal GVHD [74] and has been shown to have anti-inflammatory effects in the setting of colorectal cancer [75], pouchitis after ileal pouch-anal anastomosis [75], and liver cirrhosis [76], where *Blautia spp.* have been associated with improved outcomes. Furthermore, *Bifidobacterium* is an important health-promoting gut microbe previously shown to improve gut mucosal barrier function, and lower intestinal and plasma lipopolysaccharide (LPS) levels [77]. Consistent with their depletion from the CVID intestinal microbiota and the concomitant increase in *Gammaproteobacteria*, patients showed elevated plasma levels of LPS and sCD25, indicative of increased intestinal permeability and systemic immune activation. These features were more pronounced in the subgroup of CVID patients with immune dysregulation, associated with augmented production of pro-inflammatory cytokines [72]. These results were consistent with a separate study investigating endotoxemia in untreated CVID patients with very low IgG levels [78]. While the authors reported that LPS could contribute to T-cell dysfunction in CVID [78], interactions between the gut microbiota and systemic immune activation may likely involve mechanisms independent of LPS and Toll-like receptors, as no significant correlation was found between systemic LPS and sCD25 [72]. Similarly, other studies have reported high levels of sCD25 and sCD14 in the presence of normal LPS plasma levels [79,80]. Different factors may possibly explain the discrepancy observed, including the overall variability in LPS measurements (e.g. serum versus plasma) as well as bacteria-specific effects on gut permeability. In fact, although both CVID and IBD patients showed similarly reduced microbial diversity, this reduction in diversity correlated with endotoxemia markers in CVID but not IBD.

Microbial dysbiosis and translocation induced by the immune defect might explain immune dysregulation in different cell types [59]. Several CD4 T cell abnormalities have been documented in CVID patients, including reduction of CD4 T cell count with inversion of CD4/CD8 ratio, high T cell activation, reduced proliferation capacity in response to bacteria antigens, and/or impaired production of cytokines [81,82]. These defects may be ascribed to PD-1–associated cell exhaustion [78]. Blockade of the PD-1–PD ligand 1/2 (PDL-1/2) pathway has been associated with the restoration of bacteria-specific CD4 T cell proliferation. Importantly, PD-1 expression on T cells correlates with systemic LPS [78], supporting that microbial translocation has a role in CVID T cell pathology. The combination of IgA deficiency and perturbed microbiota may also be responsible for regulatory T cell (Treg) dysfunction in CVID. Reduced Treg frequency and impaired suppressive capacity have been frequently documented in CVID patients [83,84], likely playing key roles in the immune dysregulation and inflammatory complications in CVID. Interestingly, *Kawamoto* et al. [68] reported that expansion of $Foxp3^+$ T cells was facilitated by the maintenance of a diversified and balanced microbiota, which in turn was ensured by a $Foxp3^+$ T cell-mediated regulation of IgA diversification and selection, in a symbiotic regulatory loop. In addition, certain commensals have shown the ability to directly differentiate/activate Tregs. Colonization of germ-free mice with *Clostridium* spp. was sufficient to induce Tregs in the gut [41,85]. Furthermore, the human commensal bacterium *Bacteroides fragilis* can also induce Tregs in the mouse intestine [86].

The innate immune compartment is similarly affected in CVID patients, although the reasons for that are unclear. Dendritic cells (DCs) are reduced in the blood of patients [87,88] and exhibit multiple functional impairments which are linked to cell hyporesponsiveness and exhaustion [89–91]. In support to this, CVID plasmacytoid DCs have also been found to produce less interferon-α (IFN-α) in response to Toll-like receptors 7 and 9 *in vitro* [91,92]. DC defects are more frequently observed in patients with autoimmune-like manifestations suggesting that they are more associated with immune dysregulation than frequent bacterial infections.

For instance, direct interaction between CD40-activated DCs and B cells promotes the development of IgA-mediated mucosal immunity [63]. Reduced expression of CD40 molecules in DCs from CVID patients [89] and reduced IgA responses may contribute to gut microbial alteration in CVID. Moreover, bacterial recognition through MyD88 within follicular DCs is important for the generation of IgA + B cells [93]. Gut microbiota may also induce the expression of Retinoic Acid, BAFF, and APRIL in lamina propria DCs to trigger the development of IgA + B cells [94–96]. Therefore, intestinal microbiota composition is highly influential.

Finally, *Malamut* et al. [97] reported that treatment with IVIG did not ameliorate the gastrointestinal problems observed in CVID patients. In the small bowel of these patients, villous atrophy associated with severe malabsorption has been reported [98]. Interestingly, studies in mice showed that in the absence of B cells or IgA plasma cells, the intestinal epithelium responds to microbes by upregulating interferon-inducible immune response pathways and simultaneously repressing

Table 1
Alterations of Intestinal microbial composition in PIDs disease. Studies investigating the gut microbiota in PID patients and relative animal models. SCID, Severe Combined Immunodeficiency; OS, Omenn Syndrome; IPEX, Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked; IL10 Deficiency, Interleukin-10 Deficiency; SIgAD, Selective Immunoglobulin A Deficiency; CVID, Common Variable Immune Deficiency; AD-HIES, Autosomal Dominant Hyper IgE Syndrome; CGD, Chronic Granulomatous Disease; LAD-I deficiency, Leukocyte Adhesion Deficiency; HD, Healthy Donors; pts, patients.

Disease	Human cohort/animal studies	Major findings	Reference
SCID	IL2RG pts (n = 2)	Patients' bacterial profile pre-HSCT: ↑ *Firmicutes* and *Actinobacteria*	[87]
	RAG1 pt (n = 1)	post-HSCT: ↑ *Firmicutes* and *Proteobacteria*	
OS	Rag2R229Q/R229Q mice	↑*Proteobacteria*	[100]
IPEX	Scurfy (SF) mice	↑ *Bacteroidetes* ↓ *Lactobacillus* (*L.Reuteri*)	[107]
IL10 deficiency	IL10-/- mice	↑ *Proteobacteria* and *E. Coli* (during onset of inflammation) ↓ *Bacteroidetes* and *Firmicutes*	[116]
SIgAD	SIgAD pts (n = 21); HD (n = 34)	↑ *Firmicutes* and *Bacteroidetes* ↑ *Gammaproteobacteria* ↑ *Prevotella* ↓ *Firmicutes* (*Lachnospiraceae* and *Faecalibacterium)* ↓ *Bacteroides*	[20]
CVID	CVID pts (n = 44); HD (n = 263)	↓ *Actinobacteria* (*Bifidobacteriaceae*)	[19]
AD-HIES	AID−/− mice	↓ *Firmicutes (Christensenellaceae and Lachnospiraceae Blautia)* ↓ Deltaproteobacteria (*Desulfovibri nales* genuso *nales* genus) ↑ *bacilli* and *Gammaproteobacteria* ↑ *Clostridia* (*Lachnospiraceae Dorea* and *Lachnospiraceae Roseburia*)	
		1.↑ anaerobic flora in small intestine	[56]
		2. ↑ *Clostridium* and *Bacteroides*	[17]
	AD-HIES pts (n = 18); HD (n = 25)	Reduced diversity in oral mucosal communities: ↑ *Streptococcus oralis* and *mutans spp* (in patients with active oral candidiasis) ↓ *Neisseria*, *Porphyromonas* and *Haemophilus* ↓ *C. Parapsilosis*, *Boletus* and *Penicillium* ↑ *Capnocytophaga*	[78]
	AD-HIES pts (n = 7); HD (n = 10)	Altered microbial composition in oral swab: ↓ *Prevotella* and *Fusobacteria*	[79]
CGD	p47phox−/− *(Ncf1)* mice	Increased microbial richness ↑ *Akkermansia municiphila spp*	[188]
LAD deficiency	LAD pts (n = 5); HD (n = 12)	↓ *Actinomyces naeslundii, Rpthia dentocariosa Granulicatella adiacens spp* ↑ *Treponema, Parvimonas micre, Eubacterium brachy, Porphyromonas endodontalis spp*	[193]

metabolic functions regulated by the transcription factor Gata4 [99,100]. This shift in intestinal function leads to lipid malabsorption and decreased deposition of body fat [101]. The expression of Gata4-dependent genes, controlling lipid and carbohydrate metabolism, oxidative reduction and transport of micronutrients including vitamins, was similarly affected in CVID intestinal biopsies [101], suggesting that IgA responses are also a critical determinant of the metabolic complications in CVID [102].

2.2. Selective IgA deficiency

IgA deficiency is the most prevalent primary immunodeficiency and is characterized by low or absent serum IgA (< 0.07 g/L) with normal levels of IgG and IgM. There is a poorly defined genetic susceptibility associated with IgA deficiency. Autosomal recessive, autosomal dominant, and sporadic transmission patterns have all been observed [103]. Because of the variable inheritance patterns and the lack of an identified mendelian defect, IgA deficiency has been regarded as a heterogeneous group of genetic abnormalities, similar to CVID. In addition, associations between IgA deficiency and certain major histocompatibility complex (MHC) class haplotypes have been proposed [104]. Selective IgA deficiency (SIgAd) was for a long time considered asymptomatic, even though IgA deficiency has been epidemiologically associated with a risk for autoimmune development [105]. Recent longitudinal studies, assessing disease-associated complications more broadly, revealed that 80% of patients are indeed symptomatic [106]. Infections of the respiratory system are the most common findings in individuals with IgA deficiency [104]. These infections are mostly due to bacteria, e.g. *Haemophilus influenzae* and *Streptococcus pneumoniae*. In addition, SIgAd is associated with allergy, autoimmunity and disorders of the gastrointestinal tract. Giardiasis, malabsorption, intolerance, celiac disease, ulcerative colitis, lymphoid hyperplasia, and malign proliferation are among the associated diseases. Since the protective barrier of the gastrointestinal system is impaired in IgA deficiency, protozoa such as *Giardia lamblia* can adhere to the epithelium, proliferate and cause infection. Damage to the intestinal epithelium and impaired mucosal clearance of molecules and proteins may facilitate antibody production against certain antigens and intolerance to certain foods. As a result, patients with IgA deficiency have a higher chance of developing celiac disease [107]. Inflammatory bowel diseases, mostly ulcerative colitis, have also been reported in association with selective IgA deficiency [108]. In mice, IgA deficiency resulted in more severe DSS-induced colitis [109]. Several lines of evidence in mouse models of IgA deficiency indicate that increased colitis susceptibility is linked to an aberrant microbial composition in the gut.

2.2.1. Mild microbial ecology perturbation in IgA deficiency

Activation-induced cytidine deaminase (AID)-deficient mice, displaying impaired IgA class switch recombination, exhibited an expansion of anaerobic flora in the small intestine compared with wild-type mice, predominantly *SFB* and *Clostridium spp.*, as well as nodular hyperplasia induced by microbial antigens [69,110]. Mouse models impairing IgA secretion into the gut lumen were also associated with dysbiosis, susceptibility to DSS colitis and increased translocation of

bacterial products upon infection [111,112]. Although dysbiosis in the absence of IgA is evident in these studies, it is unclear if IgA preferentially binds to and limits certain microbes in the gut. Recently, specificity of IgA towards *Enterobacteriaceae* in the microbiota of mice was reported [109,113]. Similarly, a reduction in high-affinity IgA production, due to a deficiency in Myd88 specifically in T cells, led to significant shifts in microbial composition in the gut with marked expansion of mucolytic bacterial taxa, such as *Desulfovibrionaceae, Mucispirillum* and *Ruminococcus* [18]. From these studies it is evident that IgA plays an important role in shaping the microbiota by potentially restraining harmful inflammation-promoting bacteria. Indeed, a recent study found that colitogenic intestinal bacteria were highly coated with IgA in mice [114]. Whereas IgA-coated bacteria from individuals with IBD [114] or nutritional deficiencies [115] exacerbated respective pathologies in mice, IgA-coated bacteria from healthy humans were protective [115]. Thus, in addition to clearing invasive pathogens, IgA responses also foster colonization of beneficial microbiota [116].

Similar to what was observed in murine IgA deficiency, human IgA deficiency is not associated with extensive perturbations of gut commensal communities. *Fadlallah* et al. [73] compared the gut microbial communities in the feces of patients with IgA deficiency (n = 21) with those of age- and sex-matched healthy controls (n = 34) using a metagenomics approach. Microbiota diversity did not differ significantly between patients and controls, although the relative compositions were different. Particularly, 17 microbial species within the *Firmicutes*, *Bacteroidetes* and *Proteobacteria* (exclusively *Gammaproteobacteria,* including *E. coli*) phyla were higher in the IgA-deficient subjects. In addition, three oral commensals (*Streptococcus sanguinis*, *Veillonella parvula* and *Haemophilus parainfluenzae*) and two species of *Prevotella* were also overrepresented in the SIgAd cohort. Most bacteria depleted in IgA deficiency (13 of 14) belonged to the *Firmicutes* phylum (*Lachnospiraceae* family and *Faecalibacterium* genus) whereas one was in the *Bacteroides* phylum [73]. Overall, IgA deficiency led to depletion of some typically beneficial symbionts and expansion of pathobionts. *Faecalibacterium*, a genus well known to exert anti-inflammatory effects on the gut mucosa, is notably depleted in IBDs [117,118]. Conversely, the potentially pro-inflammatory species, *Gammaproteobacteria* and *Prevotella*, are overrepresented in SIgAd. Interestingly, gut microbiota analysis in SIgAd patients revealed ectopic localization of oral flora in the lower digestive tract, an event associated with gut inflammation in susceptible host animals [119]. Beyond describing the impact of IgA deficiency on gut microbiota composition, this study showed that SIgAd patients had IgM on the surface of intestinal microbes, supporting the possibility that secretory immunoglobulins from different isotypes can replace each other. This would also explain the mild phenotype observed in SIgAd compared to CVID patients. Likewise, IgA and IgM preferentially bound to *Clostridium*, *Bifidobacterium* and *Faecalibacterium spp.*. Some taxa, however, including members from the *Enterobacteriaceae* and *Prevotellaceae* families, were shown not to be coated with IgM [73]. These results, together with the susceptibility to enteropathogens in SIgAd patients, suggest that IgA deficiency cannot be totally compensated by IgM secretion, and that the compensating host mechanisms of IgA deficiency may be driven in different ways. The lack of IgA also induced perturbations in host systemic inflammatory versus regulatory responses. In this study [73], SIgAd patients had skewed Th17 profiles in circulating $CD4^+$ T cells which were associated with increased serum sCD14, a marker of monocyte activation. Moreover, as reported in CVID patients [78], $CD4^+$ PD-1+ cells were increased in SIgAd patients, possibly reflecting T cell exhaustion induced by persistent bacterial translocation. Nevertheless, the authors did not find correlations between the clinical status and any of the elevated immunological and translocation markers.

2.3. Hyper-IgM

The hyper-IgM syndrome (HIGM) consists of a heterogeneous group of rare disorders caused by defects in class-switch recombination, resulting in reduced levels of IgG, IgA, IgE, and impaired antibody function. Serum IgM levels are normal or elevated. X-linked HIGM is the most common form, resulting from mutations in the *CD40*LG gene. Autosomal recessive forms of HIGM due to mutations in *CD40*, *AID* and *UNG* genes have also been described [120]. Affected individuals have recurrent infections, primarily caused by encapsulated bacteria (e.g., *Streptococcus pneumoniae* and *Haemophilus influenzae*). In addition, opportunistic infections, particularly with *Pneumocystis*, *Cryptosporidium*, and *Histoplasma* are common. Chronic or protracted diarrhea occurs in over 50% of patients beginning early in life and may lead to failure to thrive [121]. *Cryptosporidium parvum*, *Giardia lambia* and *Salmonella* are frequently isolated from feces of X-HIGM patients [122]. Autoimmune complications are observed in a minority but include IBD.

In the absence of pathogens, mice that lack whole IgA (AID-deficient mice) and mice that lack only high-affinity IgA due to an SHM defect (AIDG23S-mutant mice) developed immune hyperactivation and dysbiosis-associated lymphoproliferative disease. These data suggest that only high-affinity IgA, plays a crucial role in the control of commensal gut microbiota [110]. The SFB population, which was aberrantly expanded in these knockout mice, was reduced in the presence of normal IgA levels in $AID^{-/-}$ mice. This reduction was accompanied by an increase in *Lactobacillus spp.* in the small intestine [69,110].

2.4. Hyper-IgE

Hyper-IgE syndrome (HIES) is a rare disease characterized by extremely elevated serum IgE, abnormal inflammatory processes and dysregulated immunity. Most patients with autosomal dominant HIES (AD-HIES) have mutations in the Signal Transducer and Activator of Transcription 3 (*STAT3*) gene [123]. Other mutations identified in autosomal recessive patients are found in *TYK2*, *DOCK8* and *PMG3* genes. AD-HIES patients with defects in *STAT3* alter the JAK-STAT signaling pathway affecting the induction and signaling of numerous cytokines (i.e., IL6, IL10, OSM), and the differentiation of naïve into IL17-producing CD4 + T cells [124]. Susceptibility to infection may in part be due to the defect in circulating Th17 cells, which may result in decreased neutrophil production, decreased inflammation, and increased susceptibility to *Candida albicans* and Staphylococcal infections [125]. Moreover, reduced B cells and impaired responses to T cell-dependent antigens have been reported in AD-HIES patients. Increased plasma B cell Activating Factor (BAFF) levels and reduction in BAFF receptor (BAFF-R) expression were also seen in AD-HIES [126], similar to patients with CVID. The most prominent clinical manifestations are dermatitis and recurrent infections in the lung and skin [127]. The Th17/IL17 axis plays a critical role in the surveillance of the mucosal barrier. Patients with defects in Th17/IL17 immunity are more prone to develop oral fungal infections [128,129]. Furthermore, *Conti* et *al.* [130] showed that STAT3-deficient HIES is associated with reduced salivary antifungal activity, correlating with reduced expression of specific antimicrobial effectors, including human β-defensin 2 and numerous histatins. The oral microbiomes of a large cohort of AD-HIES patients (n = 36) was investigated in detail [131]. AD-HIES patients harbored distinct mycobiome communities compared to healthy controls. Patients with active fungal infections had severe dysbiosis with dominance of *Candida albicans*. In contrast, the genus *Malassezia* was predominant in uninfected patients. AD-HIES patients had complete depletion of health-associated *C. parapsilosis, Boletus* and *Penicillium* species. Oral bacterial communities were also dysbiotic in AD-HIES, particularly in the setting of active *Candida* infections. Several common oral bacterial commensals, including *Neisseria, Porphyromonas* and *Haemophilus* had lower relative abundance in AD-HIES patients, while the genus *Capnocytophaga* was overrepresented [131]. Reduced abundance of gram-negative bacteria in the oral swabs of HIES patients, namely *Prevotella* and *Fusobacteria*, was also reported in a smaller study [132]. Microbial communities in infected patients were more dysbiotic

and enriched in the *Streptococcus* genus (*S. mutans* and *S. oralis)*. Collectively, these findings indicate a critical role for the STAT3-Th17 axis in the commensalism of *C. albicans* and for the establishment of oral bacterial communities.

Interestingly, it has been shown that selected oral streptococci can enhance *C. albicans* virulence by increasing its capacity to invade oral tissue and cause mucosal lesions [133]. It is conceivable that similar cooperative relationships between microbes might play a role in determining the increased susceptibility to candidiasis in AD-HIES. This notion is supported by another study evaluating the AD- HIES patients. *Smeekens* et *al*. [132] found that a shift of the cutaneous microbiota towards gram-negative colonization (particularly *Acinetobacter spp.*) was associated with poor immune response to *C. albicans* and *S. aureus in vitro* due to TNF and IFNγ inhibition. Although validating studies with larger cohorts of patients are warranted, these data in AD-HIES patients raise the possibility that targeting specific bacteria might have beneficial effects, even for non-bacterial infections.

2.5. Severe combined immunodeficiency

Severe combined immunodeficiency (SCID) includes a group of rare monogenic disorders that are characterized by early onset, profound block in T and B cell development [134]. SCID is rare with an overall incidence around 1 of 50,000 live births. In the absence of mature lymphocytes, adaptive immunity is abrogated, resulting in broad susceptibility to bacterial and other infections [135]. Affected children manifest severe diarrhea and malabsorption early in life. Cytomegalovirus, rotavirus and adenovirus infections are common [6]. Thus, patients with untreated SCID usually do not live beyond 6–12 months [136]. Transplantation of allogeneic hematopoietic stem cells (HSCT) can restore T/B cell development, making it the treatment of choice in SCID [135]. Once diagnosed, children with SCID receive prophylactic antibiotics and breast-feeding, which affects the normal development of gut microbiota [137]. Additionally, conditioning treatment with chemotherapy often preceding HSCT, causes mucositis and severe immunosuppression, thereby increasing the susceptibility to bacterial infections. HSCT can have life-threatening complications, such as graft versus host disease (GvHD) and bacteremia [138]. Although a variety of factors influence GvHD, the intestinal microbiota seems to be important [139]. *Lane* et *al.* described the microbiome in SCID and demonstrated that bacterial taxonomy of the gut microbiota in SCID changed over time, leading to distinct microbiome profiles pre- and post-HSCT. Despite the limited number of patients analyzed, low microbial diversity and dominance by specific species (mainly *Escherichia*, *Staphylococcus* and *Enterococcus*) characterized the pre- and post-HSCT periods [140]. In another study, the same authors highlighted specific metabolites pre-HSCT and others post-HSCT. Additional studies are required to identify the nature and the function of these bacterial metabolites in SCID patients undergoing HSCT [141]. Intestinal microbiota diversity and the identification of bacterial taxa with pathogenic or beneficial potentials might provide novel biomarkers for monitoring intestinal inflammation during HSCT. Bacterial species present at lower abundance in SCID patients may offer opportunities for bacterial targets, making specific fecal microbiota transplantation (FMT) a treatment of intestinal disease in these patients.

In addition to the typical SCID, patients with atypical SCID have residual B and T cell development and oligoclonal T cell expansion [142]. A subset of these patients present hypomorphic mutations in the *RAG* genes, causing a profound immunodeficiency associated with multisystem autoimmune–like manifestations mediated by oligoclonal self-reactive T and B cells [143–145]. Clinically, patients with Omenn Syndrome (OS) manifest with erythroderma, chronic diarrhea, lymphadenopathy, hepatosplenomegaly, eosinophilia, susceptibility to infections and failure to thrive [145]. In the last decade, our group and others have made advances in OS immunopathology [146–151]. However, it was not known whether immune dysregulation in OS led to differences in the microbiome or whether the microbiome contributed to the disease itself.

Recently, we showed that in *Rag2*$^{R229Q/R229Q}$ *mice*, the murine OS counterpart, the intestinal microbiota had a substantial role in driving immune dysregulation [152,153]. *Rag2*$^{R229Q/R229Q}$ mice manifested spontaneous IBD-like disease characterized by dominant mixed Th1/Th17 immune responses, implicated in experimental models of colitis, as well as in IBD in humans [154]. Importantly, Treg cells played a pivotal role in maintaining immune homeostasis and promoting tolerance against intestinal antigens and commensal bacteria [155]. Although Treg cells greatly accumulated at the intestinal mucosa, they were not functionally competent, further contributing to the autoimmunity observed in OS mice. *Rag2*$^{R229Q/R229Q}$ mice also exhibited a general B cell deficiency at the mucosal interfaces. Consistently, analysis of the intestinal microbiota revealed markedly reduced bacterial diversity compared to wild-type, and a concomitant relative enrichment for bacterial species within the phylum *Proteobacteria* [156]. Additionally, defects in the permeability of the gut-blood barrier were associated with high levels of endotoxin. Therefore, mucosal B cell deficiency in OS mice favors microbial access to the circulation and considerably impacts the microbial ecosystem. Long-term antibiotic treatment significantly improved intestinal, as well as systemic inflammation and normalized the elevated serum IgE, a hallmark of the disease. In particular, both mucosal and systemic pro-inflammatory Th1 and Th17 cells decreased significantly in antibiotic-reated *Rag2*$^{R229Q/R229Q}$ mice, suggesting that this pro-inflammatory skewing was microbiota-dependent. In fact, transfer of altered microbiota isolated from *Rag2*$^{R229Q/R229Q}$ mice into wild-type recipients was sufficient to induce the same Th1/Th17 phenotype, further supporting the pathogenicity of the mutant microbiota, independent of the genetic susceptibility. Overall, our results suggest that commensal microbiota are a therapeutic target for OS.

Pharmacologic gut decontamination may be a suitable strategy to reduce side effects of HSCT in OS patients. Studies revealed that complete intestinal decontamination could significantly reduce the occurrence of postoperative GVHD after HSCT [157]. Moreover, to prevent and treat complications, and ameliorate the imbalanced gut microbiome after HSCT, gut microbial interventions such as probiotics and prebiotics have been used in clinics [158]. However, further studies are needed to verify the exact mechanisms whereby these microbial interventions restrict, improve or even reverse HSCT complications in these patients.

2.6. Primary immunodeficiency associated with T regulatory and IL-10 defects

Mutations in the transcription factor FOXP3 disrupt T regulatory functions and cause the immune dysregulation, polyendocrinopathy, enteropathy X-linked (IPEX) syndrome. IPEX manifests early in life and is associated with eczema, severe enteropathy, type I diabetes, thyroiditis, hemolytic anemia, and thrombocytopenia [159]. In IPEX, intestinal lesions include GvHD-like lesions with small bowel involvement, colitis, celiac disease-like lesions and enteropathy with goblet cell depletion. The *scurfy* (SF) mouse, which has a mutation in the *Foxp3* gene, has a similar clinical phenotype. An elegant study demonstrated that SF mice manifested autoimmunity and showed an important shift in the intestinal microbiota composition with increased *Bacteriodetes* and low abundance of *Lactobacillus* [160]. Reshaping gut microbiota with one species of *Lactobacillus, L. reuteri,* extended mouse survival and inhibited multi-organ inflammation. *L. reuteri* specifically increased the relative abundance of the phylum *Firmicutes* and the genera *Lactobacillus* and *Oscillospira*, and decreased the relative abundance of the phylum *Tenericutes* and the genus *Bacteroides.* Feeding mice with *L. reuteri* restored levels of the purine metabolite inosine, which activated A_{2A} receptors in T cells to inhibit their differentiation toward a Th1/Th2 phenotype [160]. These findings indicate the feasibility of

microbiome-based adjuvant therapy in IPEX patients.

Another primary immunodeficiency affecting the gastrointestinal tract is IL-10 deficiency. IL-10 and IL-10 receptor (IL-10R) defects cause severe dysregulation of the immune system. Patients affected by these mutations present early in life with severe IBD [161]. In mice immunodeficient in IL-10, a link between the microbiome and colitis disease penetrance is clear. Spontaneous enterocolitis occurs in a microbiome-dependent manner: intestinal inflammation did not occur when $IL10^{-/-}$ mice were born and maintained in germ-free conditions [162]. Furthermore, the introduction of specific bacterial species could modulate intestinal inflammation in beneficial or harmful ways. Members of the *Lactobacillus* and *Bifidobacterium* species attenuated signs of colitis, whereas *E. faecalis* and *Helicobacter* exacerbated the intestinal disease [163–166]. Treatment of neonatal $IL10^{-/-}$ mice with antibiotics prevented the onset of colitis, indicating the crucial role of the microbiota at birth in determining disease susceptibility in later life [167,168]. Another study also reported important changes in the diversity and composition of the intestinal microbiota with a progressive decrease in microbial diversity and richness, and an increase of *Proteobacteria* and *Escherichia coli* during the onset of inflammation in $IL10^{-/-}$ mice. Significant reduction in the concentration of *Bacteroidetes* and *Firmicutes* phyla has been detected, thus reflecting the microbial changes reported in human IBD [169]. Marked reduction in the levels of *Actinobacteria* and *Verrucomicrobia* phyla was also observed. Although several studies in mouse models have proven a link between *IL10* and microbiota, these findings need to be confirmed in patients.

3. Primary immune deficiencies with defects in phagocyte function

3.1. Chronic granulomatous disease

Chronic granulomatous disease (CGD) is an inherited disorder of the NADPH oxidase 2 (NOX2) complex, responsible for the respiratory burst in phagocytess. It is characterized by recurrent and severe infections, dysregulated inflammation and autoimmunity [170]. NOX2 comprises both membrane-bound and cytosolic proteins that act upon phagocyte activation to produce reactive oxygen species (ROS), essential for the normal killing of bacteria and fungi. The catalytic glycoprotein $gp91^{phox}$ and the non-glycosylated protein $p22^{phox}$ are located in the cell membrane, forming the heterodimer $cytochrome_{b558}$. Upon phagocyte activation, the cytosolic proteins $p47^{phox}$, $p67^{phox}$, and $p40^{phox}$ translocate to $cytochrome_{b558}$ and recruit RAC1/2. This results in a conformational change of $gp91^{phox}$, which enables cytosolic NADPH to donate an electron to molecular oxygen in the phagolysosome to form superoxide ions. Superoxide ions are then used to generate ROS (hydrogen peroxide, hypochlorous acid, hydroxyl radicals) and secondary amines that are highly toxic to phagocytosed microbes [171].

Overall, CGD has an estimated incidence of between 1/200,000 and 1/250,000 live births [172]. The major genetic form of CGD is X-linked, caused by mutations in the *CYBB* gene, encoding the $gp91^{phox}$ subunit (renamed NOX2). The other forms of CGD are autosomal recessive, characterized by mutations in *CYBA*, *NCF1*, *NCF2* and *NCF4* encoding $p22^{phox}$, $p47^{phox}$, $p67^{phox}$ and $p40^{phox}$ respectively. X-CGD represents about 70% of the total cases reported to date, although in countries with high rates of consanguinity, the incidence of autosomal recessive CGD exceeds that of X-linked CGD [172].

3.1.1. Infections in CGD patients

CGD is characterized by a predisposition to bacterial and fungal infections [173]. Indeed, the majority of CGD patients are diagnosed after infections of the lung, skin, lymph node or liver, causing pneumonia, suppurative adenitis, subcutaneous abscess, liver abscess, osteomyelitis and sepsis.

The most common pathogens encountered in CGD patients are Gram-positive bacteria (e.g. *Staphylococcus aureus*), Gram-negative bacteria (e.g. *Salmonella spp., Burkholderia cepacia, Serratia marcescens, Nocardia spp.*) and fungi (e.g. *Aspergillus spp.*). Emerging pathogens in patients with CGD include also Gram-negative pathogens (e.g. *Granulibacter bethesdensis*), Gram-positive pathogens (e.g. *Actinomyces* spp.), and fungi (e.g. *Neosartorya udagawae*). These uncommon pathogens in CGD provide clues to the critical pathways and functions of NOX2 [174,175].

In addition to infections, patients with CGD frequently experience inflammatory complications, including autoimmunity [176]. Apparently, dysregulated inflammation occurs more frequently in X-linked CGD than the autosomal recessive forms (*CYBA, NCF1, NCF2* and *NCF4*). The hallmark of CGD is granulomatous inflammation. In some cases, granuloma formation is a response to active infection, but in many cases it is believed to reflect a dysregulated inflammatory response and/or inefficient degradation of inflammatory mediators and debris [177–180]. CGD granulomas can be found in multiple organs, including the brain, lungs, liver, spleen, eyes, genitourinary tract and particularly, the gastrointestinal tract.

3.1.2. Inflammatory complications: the IBD-like syndrome

A chronic inflammatory process affecting both small and large bowel is present in many CGD patients, and may precede the diagnosis of CGD and the development of infectious complications. The reported prevalence of CGD-associated IBD (CGD-IBD) ranges from 31% [181] to 88% [182]. IBD onset can be observed anytime between very early childhood (< 6 years of age) [181] and early adulthood as is sometimes the case in autosomal recessive CGD [182,183]. Gastrointestinal involvement, although initially thought to be more common in X-linked CGD, is actually just as prevalent in autosomal recessive CGD and not correlated with residual ROS levels [6,184]. CGD-IBD has features common to both Crohn disease (CD) and ulcerative colitis (UC). Patients may present with perirectal disease, gastrointestinal tract obstruction and recurrent diarrhea. The colon is the most frequently affected site, displaying a thickened bowel wall, pancolitis and pseudopolyps, whereas the histology reveals submucosal edema, crypt abscesses, inflammatory cell infiltration, cryptitis, epithelioid granulomas in the muscularis and large pigment-laden histiocytes in the lamina propria [183,185,186]. Decreased NOX2 activity below the threshold leading to CGD, which is sometimes observed in female carriers can also be associated with very early onset (VEO) IBD (< 6 years of age) [187,188]. Moreover, several genome-wide association studies have identified functionally altered variants in NOX2 complex components in patients with VEOIBD and have linked these variants to increased risk of adult-onset IBD [189,190]. Together, these data highlight an important role for ROS and NOX2 activity in both CGD-associated and conventional IBD pathogenesis.

3.1.3. Gut resident polymorphonuclear leukocytes and NADPH oxidase in the maintenance of intestinal homeostasis

Because they provide the first line of defense to infection, intestinal polymorphonuclear leukocytes (PMNs) are strategically positioned throughout the subepithelial lamina propria to ensure immune response against ingested pathogens. PMNs frequently interact with beneficial commensal microbes and food antigens, posing the need of balancing inflammatory with tolerogenic responses. In fact, a number of studies now indicate that PMNs provide signals that limit inflammatory reaction and promote mucosal homeostasis. Macrophages and DCs (phenotype and ontogeny reviewed in Ref. [191]), have distinct and complementary roles. At steady state, both DCs and macrophages maintain immune tolerance against local commensal bacteria and antigens, remaining hyporesponsive to TLR stimulation as well as inducing and expanding intestinal T cells with regulatory function [192]. Upon pathogen encounter and microbial activation, DCs migrate from the intestinal lamina propria to the draining lymph nodes to activate effector T and B-cell responses. In contrast, macrophages do not enter the

lymphatics and instead initiate a local inflammatory response through phagocytosis of bacteria and production of cytokines that promote leukocyte recruitment. The induction of these immune circuits by PMNs usually results in the restoration of tissue homeostasis. However, when aberrantly induced or directed against persistent stimuli, they can lead to intestinal immunopathology and chronic inflammatory diseases. Specifically, PMN-derived NOX2 can affect numerous pathways relevant to IBD, including processing and clearance of microbial products and antigens, neutrophil accumulation, transcriptional factor activation, cytokine responses and adaptive immunity.

ROS production by NOX2 NADPH oxidase activity is among the earliest and the most robust defenses against pathogens. It is therefore not surprising that a number of microbes have evolved mechanisms to modulate ROS production by NOX2 [193]. PMNs express a group of receptors that can induce the formation and generation of ROS. Activation of integrin and Fc receptors leads to complex intracellular signal transduction pathways that can robustly activate the NADPH oxidase complex. Some members of the G-protein-coupled receptors (GPCRs) family, specifically formyl receptors, can also directly activate the NOX2 complex, although to a lesser extent. Ligand binding to Toll-like Receptors, TNFRs, and some members of GPCRs can prime neutrophils, whereby the NADPH oxidase is more susceptible to activation by a secondary stimulus [194]. This extra level of regulation ensures that reactive oxygen species are produced at the right time and place and only during active infection. There is evidence that defective bacterial killing by macrophages and monocytes might contribute to IBD susceptibility. Phagocytes from patients with Crohn disease generate lower levels of ROS and exhibit impaired phagocytosis and bacterial killing compared to phagocytes from healthy individuals [195,196]. This deficiency leads to prolonged bacterial persistence and exacerbated pro-inflammatory responses. Moreover, NOX2 is upregulated in mucosal macrophages from inflamed intestinal tissue of patients with CD [197].

In addition to a direct antimicrobial effect mediated by oxidative damage, NOX2 activation plays a role in the mobilization of other host microbicidal factors from the phagosome, such as proteases and elastases, targeting them to the pathogens for degradation [198]. Another host antimicrobial process activated by NOX2-derived ROS is the formation of neutrophil extracellular traps (NETs), a network of extracellular fibers primarily composed of chromatin from neutrophils that co-localize with cytosolic and granular proteins [199]. NETosis is triggered in response to infection and to conditions mimicking sepsis that can mediate host defense through binding to microbes preventing dissemination, microbial factors degradation and killing of pathogens [200]. As such, a number of NET components have antimicrobial activity (e.g. myeloperoxidase and calprotectin) [201,202]. Interestingly, neutrophils from CGD patients are defective in NETosis, further implicating the NOX2 complex in this antimicrobial response [200]. Macrophage and neutrophil NOX2 also regulates acute inflammation, which might explain the hyperinflammation seen in CGD patients. In particular, NOX2 activation can limit inflammation and injury by inducing neutrophil apoptosis. Efferocytosis, the up-take of apoptotic cells, conducted by macrophages through phosphatidyl serine receptors, is reduced in CGD [203]. CGD macrophages are also severely compromised in their ability to produce anti-inflammatory mediators due to a delay in apoptotic debris clearance [204]. NOX2 can also modulate inflammation by regulation of transcription factors, for example NF-kB [205]. The NOX2 complex is also involved in the control of adaptive immunity at multiple levels, including antigen presentation and cross-signaling to T- and B-lymphocytes. NOX2 expressed in DCs is recruited to early phagosomes leading to sustained production of low ROS levels and alkalinization of phagosomal lumen [206,207]. The recruitment of NOX2 can prevent acidification of phagosomes, limiting antigen degradation and enhancing antigen presentation, including cross-presentation [206–208]. MHC class I–restricted $CD8^+$ memory T cells failed to be generated in NOX2-deficient mice, due to defective DC endosomal alkalinization and autophagy. In contrast, the MHC class II pathway leading to $CD4^+$ T cell activation operated normally in CGD [209], indicating involvement of distinct intracellular pathways for T-cell priming. Additional studies indicate that ROS modulate the outcome of the T cell response. Particularly, T cells activated in the presence of NOX2-deficient DCs exhibit an altered differentiation profile and a skewed polarization towards a Th1- response [210]. Macrophages can modulate T-cell responses by producing ROS and can induce T regulatory cells in a ROS-dependent fashion. In agreement, NADPH deficiency has been associated with defective T regulatory cell induction and increased interleukin (IL)-23 and Th17 response [211,212]. Augmented IL-23/IL-17A and attenuated Treg responses, induced in NOX2-deficiency, may account for the high frequency of IBD in CGD. In fact, increased expression of IL-17 and IL-23 has been reported in IBD patients [213], and polymorphisms in the IL-23R gene have been associated with susceptibility to Crohn disease [214,215]. NOX2 activation induced by Dectin-1 ligation might be important for dampening IL-17 responses to β-glucan (eg. from *Candida* species colonizing the bowel or foods) in the bowel mucosa and protect from the risk of IBD [216]. Autophagy defects resulting in inflammation appear to be a key feature in the pathogenesis of Crohn colitis [217]. Moreover, loss-of-function polymorphisms in the autophagy genes ATG16L1 and IRGM increase susceptibility to Crohn disease [218,219], and the risk allele is associated with increased production of IL-1β [220]. Given the suggested role for NADPH-derived ROS in autophagy [221], a defective autophagic process responsible for hyperproduction of IL-1β is consistent with NADPH deficiency [222]. Interestingly, blocking the IL-1R with anakinra not only reduced IL-1β production and restored autophagy in CGD mice but also decreased neutrophil recruitment and Th17 responses [222]. Expression of ROS also occurs in lymphocytes, where the role of the enzyme is still poorly understood. In T cells NOX2 is activated by T cell receptor (TCR) stimulation [223]. NOX-deficient T cells showed enhanced activation of the kinase Erk and a relative increase in T helper type 1 cytokine secretion. Besides myeloid cells, NOX2 also regulates MHCII expression on B cells [224]. Mouse studies showed a direct relation between the B cell stimulation and the production of ROS. Lower activity of the NADPH oxidase could impair B cell receptor (BCR) signal strength, reducing activation and proliferation of B cells in response to surface immunoglobulin cross-linking [225,226]. Consistently, CGD patients had defective B cell compartments in terms of frequencies of memory B cells, responses to *in vitro* stimulation and maintenance of long-term antigen-specific memory [227,228]. Maintenance of intestinal homeostasis requires also massive generation of mucosal IgA by B cells of the adaptive immune system, a process in which PMNs have an essential role. However, because inhibition of NADPH oxidase–dependent early ROS production impairs B-cell activation and differentiation [229], defective NOX2 in B cells may account for the IgA deficiency sometimes seen in CGD patients [230].

PMNs can also significantly influence the metabolism of the intestinal mucosa, modifying oxygen's availability. Compared with other mucosal tissues, the healthy intestine is relatively hypoxic [231,232]. The low-O_2 environment is critical to ensure the basal expression, by epithelial cells, of antimicrobial peptides and proteins that contribute to effective mucosal barrier function [233,234]. This “physiologic hypoxia” enables microbial production of short-chain fatty acids (SCFAs; e.g. butyrate, propionate, and acetate), which conversely sustains oxygen consumption [234]. Utilization of oxygen, via tissue metabolism, increases during inflammation and is a key component of the epithelial restitution response during an effective inflammatory resolution (“inflammatory hypoxia”) [235]. The hypoxia-inducible factor-1 (HIF-1) is the major molecular mechanism coordinating the epithelial homeostatic transcriptional response to low-O_2 environments [236]. It has been shown that PMNs play a fundamental role in the epithelial response to mucosal inflammation in ways that promote the stabilization of HIF-1 [237]. These studies demonstrated that PMNs recruited at the site of inflammation induced local O_2 depletion in a NADPH-dependent manner, thus inducing in the surrounding epithelial

cells an HIF-1-dependent transcription of barrier-related genes [238]. HIF-1 stabilization by PMNs could also regulate the balance between regulatory and Th17 T cell responses. Indeed, *Dang* et al. showed that HIF-1 enhances Th17 differentiation whereas it attenuates Treg development by binding Foxp3 and targeting it for proteasomal degradation [239].

3.1.4. Microbiota and colitis susceptibility in NOX2-deficent mice

ROS produced by the NOX2 complex during colitis has also been investigated in CGD mice. *Cybb* knockout mice do not develop spontaneous IBD. Nox2 ($gp91^{phox}$)-deficient mice were protected against the mucosal damage induced by dextran sodium sulfate (DSS) and/or *C. rodentium* induced colitis [240], but developed severe colitis in the TNBS model [237]. They displayed enhanced PMNs infiltration, diminished inflammatory hypoxia and increased microbial invasion [237]. Mice harboring a point mutation in *Ncf1* had increased susceptibility to chronic DSS colitis [241], while *Ncf1* knockout mice did not have increased susceptibility to acute DSS colitis [242]. Similarly, $p22^{phox}$-deficiency (including selective intestinal $p22^{phox}$ deficiency) was found to be protective in intestinal infection with *C. rodentium* and *Listeria monocytogenes* through a mechanism involving intestinal ROS-mediated enrichment of H_2O_2-producing taxa in the intestinal flora [243]. In contrast, colitis susceptibility was found to be increased in $p40^{phox}$-deficient mice using both acute DSS and anti-CD40-induced colitis models [244]. As IBD development is not only associated with genetic susceptibility but also with environmental factors, some of the apparent inconsistencies in animal studies might be related to different housing conditions, nutrition or commensal communities present. The involvement of intestinal microbiome in driving IBD susceptibility in the context of NOX2 complex-deficiency has been recently addressed by our work [245]. Although *Ncf1* knockout mice did not spontaneously develop colitis, they had increased susceptibility to acute DSS colitis, which was associated with a distinct colonic transcript and microbiome signature [245]. Naïve *Ncf1* knockout mice had increased microbial richness, as well as increased abundance of *Akkermansia muciniphila*, a Gram-negative intestinal mucolytic bacterium that is reduced in IBD patients and is protective in experimentally-induced colitis [246]. After DSS colitis induction, *A. muciniphila* was no longer more abundant in $p47^{phox}$ -deficient mice. Surprisingly, neither restoring phagocyte ROS production nor exposing *Ncf1* knockout mice to wild-type fecal matter protected from DSS colitis development. In contrast, modifying the intestinal microbiota from birth with heterozygous breeding, significantly reduced colitis susceptibility in CGD mice. These results suggest that although phagocyte-derived ROS modulates intestinal microbiomic and transcriptomic signatures, composition of the intestinal microbiome at birth has a significant impact on susceptibility to intestinal inflammation in itself or as it evolved in the setting of deficient phagocyte-derived ROS [245].

3.2. Leukocyte adhesion deficiency

The neutrophils' ability to transmigrate to sites of infection and eliminate pathogens relies on an adhesive interaction between the cell surface glycoproteins, integrins and selectins, and the endothelium, tissue matrix and microbes. Leukocyte adhesion deficiency (LAD) is a group of autosomal recessive immunodeficiencies resulting from defects in these important functions. The most common and first described LAD subtype is LAD1, caused by genetic defects in CD18 (*ITGB2*), the common chain of the β2 integrin family, leading in very low or no expression of all β2 integrins [247]. LAD-1 neutrophils have profound adhesive and motility defects. Patients present with recurrent infections whose severity can vary depending on residual expression of integrins. Infections of the skin, bowel, upper and lower airways, and perirectal area and septicemia usually caused by *Staphylococcus aureus* or gram-negative enteric organisms, most notably *Pseudomonas* species, are common [248]. Other rare subgroups include LAD type 2 (LAD2) and type 3 (LAD3). LAD2 results from mutations in the Golgi GDP-fucose membrane transporter, leading to a generalized loss of expression of fucosylated glycans on the cell surface [247]. Therefore, LAD2 neutrophils are unable to bind to E− and P-selectin receptors on the endothelium. Infections in LAD2 are less severe than in LAD1 and LAD3. LAD3 is caused by mutations in *FERMT3*, which encodes kindlin-3, a protein that binds β integrin tails [247]. LAD3 patients exhibit severe recurrent infections and leukocytosis, similar to LAD1. LAD1 is associated with a severe destructive periodontitis, initially ascribed to invasive infection. However, recent studies in LAD1 patients and mice identified dysregulated IL-23/IL-17 inflammation as the critical mediator of periodontal destruction and increased oral bacterial burden [249]. *Moutsopoulos* et al. [250] described the LAD1 subgingival microbiome, marked by depletion of health-associated bacterial species, such as *Actinomyces naeslundii*, *Rothia dentocariosa* and *Granulicatella adiacens,* and a concomitant enrichment in the periodontitis-associated bacteria *Treponema spp, Parvimonas micre, Eubacterium brachy* and *Porphyromonas endodontalis*. Compared with healthy individuals and those with aggressive periodontitis unassociated with LAD1, the oral microbiome of LAD1 patients showed the unique presence of *Pseudomonas aeruginosa* and *Leptotrichia buccalis*, bacteria associated with severe infections in immunocompromised patients [251]. In particular, skin infections by *P. aeruginosa* have been reported in LAD1 patients and linked to IL-23-related inflammation [252,253]. How colonization with *P. aeruginosa* in the oral cavity may relate to systemic infections remains to be determined. However, the evidence of LPS translocation within the inflammatory lesions in LAD1, despite antibiotics, suggests that bacterial product represent a continuous trigger for local immunopathology. Consistently, inactivated subgingival plaque from LAD1 patients induced IL-23 mediated inflammatory responses *in vitro* and *in vivo* [250], pointing to the IL-23/IL-17 axis as critical in LAD-associated periodontitis.

4. Skin microbiota in cutaneous manifestations of PID

The skin provides the first line of defense for several environmental challenges. A large number of bacteria on the skin surface protect it from bacterial superinfections and contribute to homeostasis by modulating cutaneous immunity [254]. A well-coordinated network of epithelial and immune cells continuously recognizes and responds to commensal antigens even in the absence of skin barrier damage. Studies in patients and mouse models showed that skin commensals modulate the expression of several innate and adaptive pathways involved in host defense. Keratinocytes sense the skin microbiota via pattern recognition receptors (PRRs) and promptly initiate innate responses, resulting in the secretion of antimicrobial peptides (AMPs), cytokines and chemokines [255]. Multiple families of AMPs dominate the human skin, especially cathelicidin and B-defensins. The induction of AMPs ensures rapidly the killing and the inactivation of a huge range of pathogens. Complement, a central member of the innate immunity, is also modulated by skin microbes [256]. Several commensals in turn amplify innate immunity by activation of distinct signaling pathways. *Staphylococcus epidermis*, a normal skin commensal, seems to modulate innate responses through the production of phenol-soluble modulins that can selectively suppress skin pathogens, including S. *aureus* and *Group A Streptococcus,* and cooperate with AMPs to enhance killing [257,258]. Additionally, *S. epidermis* triggers keratinocyte-mediated AMP induction via a TLR2 dependent mechanism [259]. Skin commensals also modulate adaptive immune responses. Skin microbes potentially amplify the dermal T cells' ability to produce cytokines, essential for host defense [260]. Another study highlights the contribution of specific bacterial species to trigger T cell immune responses by a coordinated action of skin resident dendritic cells [261]. Recently, mouse models showed that skin colonization during a defined window of neonatal life is responsible for recruitment of Tregs [262]. Influx of highly activated Tregs into neonatal skin, but not in adults, enables establishment of

commensal-specific T cell tolerance, preventing tissue inflammation [263]. Skin infections characterize several PIDs. However, non-infectious cutaneous manifestations have also been found in many of these disorders, including cutaneous granuloma, dysplasia of skin, hair, and nails, eczematous lesions, autoimmune conditions and frank vasculitis [264]. Skin infections involving bacteria include folliculitis, abscesses, furunculosis, impetigo, or pyoderma gangrenosum. Pyogenic infections of the skin are the first and most common skin manifestation in PIDs, especially in hyper IgE syndromes and antibody deficiencies [264]. Eczematous lesions are considered the second most common presentation in PIDs, occurring in 19% of patients [265]. Some PIDs afflicted with eczema include hyper IgE syndrome, Wiskott-Aldrich Syndrome (WAS), and IgA deficiency (IgAd). Exfoliated erythroderma in the neonatal period is common in patients with OS [143,145]. Autoimmune dermatoses such as vitiligo and alopecia are more prevalence in several adaptive PIDs, including SCID [266,267] and IgAD [268].

The first studies on the skin microbiome with PID involved patients with chronic mucocutaneous candidiasis (CMC), caused by dominant gain of function mutations in *STAT1* or dominant negative mutations in *STAT3* [132]. In both cases, decreased Th1 and Th17 cell-mediated immune responses result in increased susceptibility to *Staphylococcus* and *Candida* species [269,270]. The analysis of skin microbiome in patients with STAT1/STAT3 defects revealed an important shift from normal to Gram-negative microbial flora, particularly of *Acinetobacter* species, whereas *Corynebacteria* were underrepresented (see Table 2). *Oh* et al., characterized the bacterial and fungal microbiota of several groups of PIDs, including STAT3 deficiency, WAS syndrome and dedicator of cytokinesis protein 8 (DOCK8) syndrome [271]. Although these disorders have different genetics and extra-cutaneous manifestations, all patients had atopic dermatitis (AD)-like eczema. DOCK8 deficiency impairs T cell differentiation, including Th17 cells and is clinically associated with recurrent sinopulmonary infections, eczema, staphylococcal skin infections, persistent viral infections of the skin, and a predisposition to malignancies [272]. WAS syndrome results from X-linked recessive mutations in WAS. WAS protein (WASP) has cytoskeletal functions that are affected in WAS leading to T- and B-lymphocyte dysfunction in locomotion, signaling, and immune synapse formation [273]. WAS patients manifest eczema, thrombocytopenia, neutropenia, and a predisposition to autoimmunity and malignancy. Microbial colonization with *Clostridium* species and *Serratia marcescens* was observed in PID skin compared to healthy controls. Fungal colonization by *Candida albicans* and *Aspergillus* spp dominated the skins of PID patients, suggesting that PIDs increase the colonization by atypical microbiota. These works focused heavily on the characterization of the skin microbiome diversity and composition in several PIDs. However, the cellular and molecular mechanisms underlying the host-microbe interactions remain to be explored. It might be essential to elucidate the full-range of cutaneous responses evoked by the microbiota and the exact contribution of skin microbes to disease development and progression. Proper identification of the complex host-microbiota interactions might be instrumental for better understanding PID pathogenesis and developing novel therapeutic strategies.

Table 2
Skin microbial and fungal dysbiosis in PIDs disease. Studies investigating the skin microbiota in PID patients. AD-HIES, autosomal dominant Hyper IgE syndrome; AR-HIES, autosomal recessive hyper IgE syndromE; WAS, Wiskott Aldrich syndrome; HD, healthy donor.

Disease	Human cohort/ animal studies	Major findings	Reference
AD-HIES	AD-HIES pts (n = 7) HD (n = 10)	↓ *Corynebacterium* ↑ *Acinetobacter*	[79]
HIES	STAT3-AD-HIES pts (n = 25) DOCK8-AR-HIES pts (n = 6) HD (n = 49)	STAT3-HIES cohort ↑ *Serratia Marcescence* spp ↑ *Anaerococcus,Finegoldiaand/or Peptoniphilus* ↑ *S. Epidermidis spp* ↓ *Porphyromonas* and/or *Cloacibacterium* ↓ *Propionibacterium* Fungi: ↓ *Malassezia* ↑ *Aspergillus* and *Candida* DOCK8-HIES cohort ↑ *Clostridiales and S.epidermidis*	[214]
WAS	WAS pts (n = 10)	↑ *Propionibacterium* (beta diversity similar to the HD)	[214]

4.1. The gut-skin axis: a perspective

There is evidence supporting the existence of communication axes between organs, such as gut-skin axis. For example, atopic dermatitis and rosacea are both associated with marked alterations in gut barrier and in intestinal microbiota [274,275], suggesting that not only the local skin microbiota influences the disease pathogenesis. Dysbiosis is a hallmark of inflammatory bowel disease or celiac disease, which are also often associated with cutaneous inflammation [276,277]. Interestingly, gut dysbiosis was also found in patients with psoriasis and psoriatic arthritis (PsA), implying a possible link between skin disease and gut microbiota. In particular, *Codoñer* et al. [278] reported the existence of a specific "psoriatic core intestinal microbiome" in patients with psoriasis, described by increased proportion of *Faecalibacterium* and decrease proportion of *Bacteroides* [278]. Psoriatic arthritis can be associated with both psoriasis and IBD, suggesting an etiologic overlap between the joint inflammation and both gut and skin pathology, in which the intestinal microbiota may be the common mediator. In support to this, it is noteworthy that patients with psoriasis and PsA have decreased diversity compared to healthy individuals, but the microbiota profile of those with PsA resembled patients with IBD, characterized by a significant less representation of *Akkermansia* and *Ruminococcus* species [279].

How the imbalance of the bacterial communities may contribute to the disease onset remains however to be clarified. Studies in mouse models indicate that antibiotic-driven perturbation of the intestinal microbiota in neonatal life increases the susceptibility and the severity of psoriasis, providing important evidence for further investigation [280]. Skin involvement represents also a characteristic feature of patients with systemic sclerosis (SSc, also called scleroderma), an autoimmune disease characterized by immunological abnormalities, vascular lesions and extensive skin fibrosis accompanied by loss of cutaneous elasticity [281]. Interestingly, after the skin, the intestine is the organ most common affected in SSc [282]. Moreover, intestinal dysbiosis has been associated to SSc and its extra-intestinal clinical manifestations in different studies [281,283,284], although the causality remains to be documented. Several PID patients manifest intestinal disorders associated with skin co-morbidities. Children affected by WAS can develop IBD or IBD-like gastroenterocolitis [285,286]. At the same time, cutaneous manifestations are common in WAS patients, especially those similar to atopic dermatitis [287]. Patients with mutations in IL-10 or its receptor can develop early onset enterocolitis [161] and extensive rash on face and scalp [288]. Intestinal and cutaneous granulomas occur in CGD patients [289,290]. Intestinal and skin lesions also occur in SCID patients, sometimes due to GvHD effected by maternal cells [291]. Patients with OS have autoimmunity manifesting as IBD-like illness and cutaneous lesions [292]. Approximately 25% of patients affected by the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) suffer from gastrointestinal manifestations, including autoimmune hepatitis, atrophic gastritis with or without pernicious anemia (Biermer disease), intestinal infections, and malabsorption [293]. Moreover, cutaneous autoimmune manifestations such as vitiligo and alopecia are frequent in APECED patients. To date, the mechanism underlying the interaction between gut microbiota and

skin disorders is largely unknown. However, this complex dialogue might involve several messengers including components and/or products of the intestinal microbiota that could have access to the circulation, affecting distant sites. Indeed, the gut microbiota produces diverse metabolic products from the anaerobic fermentation of exogenous indigested dietary components that reach the colon, as well as endogenous compounds that are generated by the host and the microbes [294]. Free phenol and p-cresol, metabolic products of aromatic amino acids, can be released in case of disrupted intestinal barrier integrity, gaining access to the circulation, preferentially accumulating in the skin and impairing keratinization, thereby disrupting skin homeostasis [295]. The DNA of intestinal bacteria has been isolated from the peripheral blood of psoriatic patients, indicating a direct link between the gut microbiome and cutaneous homeostasis [296]. The interaction can also be demonstrated by the influence that the intestinal microbiome has on the composition and the diversity of the skin microbiome. Specific short-chain fatty acids (SCFAs), including butyrate, propionate and acetate, have pivotal roles in determining specific skin bacterial strains, ultimately modulating immune responses at the cutaneous level. Propionic acid produced by intestinal *Propionibacterium* can have antimicrobial effects against the community-acquired methicillin-resistant *Staphylococcus aureus*, present at the skin surface [297]. The cellular and molecular mechanisms whereby gut inflammation is linked to skin disorders remain unexplored. In celiac disease, the generation of circulating antibodies, produced by the intestinal immune reaction to gluten, triggers inflammation and dermatitis [298], confirming that immune cells traffic in and out the skin compartment. Moreover, cutaneous exposure to food antigens reprograms gut homing effector T cells in lymph nodes to express skin homing receptors, eliciting skin inflammation [299]. The possibility that gut derived T cells could be reprogrammed to express skin homing potential, thus driving skin inflammation and autoimmunity, might represent a novel interesting mechanism to explore in PIDs.

Likewise, inflammatory reactions arising at the cutaneous barrier might evolve and contribute to pathologies in other organs, including the gut. The skin is in direct contact with several environmental triggers and is inhabited by and constantly exposed to microorganisms. In particular, changes in the resident communities could perturb the overall ecosystem to induce disease conditions, even in the absence of pathogen colonization. Exposure to allergens or irritants can also damage the integrity of the cutaneous barrier, triggering local inflammatory reactions. The possibility that dermal T cells could traffic outside the cutaneous compartment, eliciting systemic inflammation represents another possible pathomechanism in PIDs. The coexistence of skin and gut co-morbidities is common in PID patients and may be important for exploring novel therapeutic approaches. The possibility to manage the cutaneous disorders with a manipulation of the intestinal microbiota might also represent an interesting prospective. Studies on atopic dermatitis reveal that oral administration of metabolites could affect skin disease by modulating anti-allergic and anti-inflammatory effects. In particular, in murine experiments, the administration of linoleic acid and 10-hydroxy-cis-12-octadecenoic acid alleviates the symptoms of atopic dermatitis and modulates intestinal microbiota. Moreover, in rosacea, the eradication of associated intestinal bacterial overgrowth results in a significant regression of cutaneous lesions [275]. On the other side, it is foreseeable to speculate that certain metabolites produced by the skin microbiota may offer benefit at distant sites, including gastrointestinal tract. Further studies are necessary to understand which microbes are involved in this complex interaction and the relative mechanism of action.

5. Conclusions

Although only a few studies of the microbiome in primary immunodeficiencies have been performed so far, this field is rapidly expanding. Patients with PIDs have taught us the host cells and pathways that are essential for immune protection at barrier sites while uncovering non-redundant pathways required for intestinal colonization by critical commensals.

Gut microbial communities in PID patients differ significantly from those in health in terms of diversity and composition. One unifying characteristic of the PID microbiome is the depletion of species typically associated with health. Health-associated communities in the gastrointestinal tract have been shown to promote homeostasis while protecting from infection in different ways. Intestinal commensals directly inhibit growth of pathogenic bacteria, activate innate immune mechanisms to suppress competing microbes, tolerate commensals and stimulate responses that maintain epithelial barrier integrity. Their alteration may underlie aberrant immune responses in PIDs. In addition to a dearth of beneficial species, the microbiota of PID patients exhibit an enrichment or dominance of pro-inflammatory species. Future studies in larger cohorts of patients could identify whether specific genetic defects are linked to specific patterns of microbiome composition or whether they help explain clinical heterogeneity in PIDs. Another common trait is the lipopolysaccharide (LPS) translocation within the inflammatory lesions and in the systemic circulation of patients with PID. Bacterial LPS has been linked to chronic immune activation and immune dysregulation. Interestingly, structure-function differences in microbiota-derived LPS have been associated with alterations in their capacity to elicit innate immune responses, and may thus preclude aspects of immune education in some individuals but not in others [53]. It will be important to evaluate whether variation in microbiome LPS immunogenicity contributes to cause autoimmunity in different PIDs.

The study of the microbiome in PID patients with active infection has provided crucial information on how microbial interactions and co-occurrence contribute to disease pathogenesis. A broad panel of viruses enhances pathobiont colonization in both adults and children. Whether pathobionts enhance viral acquisition and replication, remains to be shown [300]. These cooperative inter-kingdom relationships may occur more frequently in PIDs than proven thus far, and be responsible for disease susceptibility or secondary infections in affected patients. Research efforts in this context might also provide us with information of predictive and potentially preventive value. In addition, experimental *in vitro* models and animal challenge models could help to obtain mechanistic insight into the role of specific (groups of) bacteria in ecosystem behavior and host immunity.

Study of microbiota in pediatric PID patients has a few limitations. Firstly, the composition of the gut microbiome is unstable in infancy [301], with many environmental factors determining its development including mode of delivery, method of feeding, and neonatal hospitalization [302]. Therefore, comparison between PID patients with or without immune dysregulation might be more valuable than comparison with healthy age-matched controls.

Secondly, PID patients are frequently treated with antimicrobials to manage or prevent chronic or recurrent infection. The specific effect of long-term antibiotic use on the diversity of the human microbiome is still not sufficiently understood, especially not in relation to immune dysregulation. Some studies described long-term effects of antibiotic use on the microbiome in immune competent individuals [303,304] and antibiotic use has to be considered as a potential cofounder when studying the microbiome in immunodeficiency.

Given the observed connections between gut microbiota composition and PIDs, the potential use of dietary intervention to correct dysbiotic flora may hold promise. Based on the microbiota characteristics of PID patients a strategy could be to reconstitute ‘missing health microbes’ by administration of pre- and probiotics. To fully realize the gut microbiota as a target for and an instrument of therapy, we need to explore whether certain microbes can modulate systemic inflammation in immune deficiencies, as well as the mechanisms for such immunomodulatory effects.

Conflicts of interest

The authors declare that no conflicts of interest exist.

Footnote

Alpha diversity (Chao1): a measure for the diversity/richness of a microbial population, reflecting the number of different taxa observed within each sample, as well as their respective prevalence.

Beta diversity: a measure for the diversity/richness of a microbial population between different individuals. It also takes into account the number of different taxa as well as their respective prevalence.

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List of abbreviations

AID	activation-induced cytidine deaminase
AMPs	antimicrobial peptides
APECED	autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
APRIL	A proliferation-inducing ligand
BAFF	B cell activating factor
CD	crohn's disease
CGD	chronic granulomatous disease
CMC	chronic mucocutaneous candidiasis
CVID	common variable immunodeficiency
DC	dendritic cell
DOCK8	dedicator of cytokinesis protein 8
DSS	dextran sodium sulfate
FMT	faecal microbiota transplantation
GVHD	graft versus host disease
IBD	inflammatory bowel disease
HIES	Hyper-IgE syndrome
HIGM	hyper-IgM syndrome
HSCT	hematopoietic stem cell transplantation
IPEX	X-linked immune dysregulation, polyendocrinopathy, enteropathy syndrome
IVIG	intravenous immunoglobulin
LAD	leukocyte adhesion deficiency
LPS	lipopolysaccharide
MHC	major histocompatibility complex
NADPH	nicotinamide adenine dinucleotide phosphate
NETs	neutrophil extracellular traps
NLRP	NOD-like receptor
OS	Omenn Syndrome
PID	primary immunodeficiency disorder
PMN	polymorphonuclear leukocytes
PRRs	pattern recognition receptors
ROS	reactive oxygen species
SCFAs	short-chain fatty acids
SCID	severe combined immunodeficiency
SFB	segmented filamentous bacteria
SHM	somatic hypermutation
SIgAd	selective IgA deficiency
STAT	Signal transduced and activator of transcription
Th	T helper cells
TLR	toll-like receptor
Tregs	T regulatory cells
UC	ulcerative colitis
WAS	Wiskott-Aldrich Syndrome

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