Gut Microbiota in Primary Immunodeficiencies

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Inborn errors of immunity (IEI) are a group of disorders that are mostly caused by genetic mutations affecting immune host defense and immune regulation. Although IEI present with a wide spectrum of clinical features, in about one third of them various degrees of gastrointestinal (GI) involvement have been described and for some IEI the GI manifestations represent the main and peculiar clinical feature. The microbiome plays critical roles in the education and function of the host's innate and adaptive immune system, and imbalances in microbiota-immunity interactions can contribute to intestinal pathogenesis. Microbial dysbiosis combined to the impairment of immunosurveillance and immune dysfunction in IEI, may favor mucosal permeability and lead to inflammation. Here we review how immune homeostasis between commensals and the host is established in the gut, and how these mechanisms can be disrupted in the context of primary immunodeficiencies. Additionally, we highlight key aspects of the first studies on gut microbiome in patients affected by IEI and discuss how gut microbiome could be harnessed as a therapeutic approach in these diseases.

Keywords: gut microbiota ; inborn errors of immunity ; primary immunodeficiencies ; immune dysregulation ; dysbiosis ; gastrointestinal pathology

1. Gut Microbiota–Host Interactions in Human Inborn Errors of Immunity

Monogenic diseases affecting the immune system represent unique models to dissect gene functions and biological pathways, and may therefore provide important insights into the mechanisms of how the immune system works *in vivo*. Several IEI affect the immunological pathways involved in the above-described mechanisms of gut microbiota–host interactions, disrupting intestinal homeostasis. Interestingly, while microbiota perturbations in polygenic inflammatory bowel disease (IBD) can have a complex etiology, dysbiosis in patients with IEI is driven primarily by the gene defects.

In order to retrieve all publications analyzing gut microbiota-host interactions in human IEI, the literature review has been performed employing EMBASE, Pubmed, Scopus and Web of Science databases. The search strategy was performed using a free-text search (keywords: inborn errors of immunity, primary immunodeficiency, microbiota, microbiome, dysbiosis, gut, intestinal homeostasis) and thesaurus descriptors search (MeSH and Emtree), adapted for all the selected databases. We searched all articles published up to December 2020. The inclusion criteria for eligible articles were the following: publication in peer-reviewed journals and the English language. Articles were excluded by title, abstract, or full text for irrelevance to the analyzed topic. Lastly, to identify further studies that met the inclusion criteria, the references of the selected articles were also reviewed. Table 1 shows a summary of the available evidence.

Table 1. Evidence of the role of gut microbiota–host interactions in human inborn errors of immunity.

Disease	Genetic Defect	Inheritance	Main Findings	Reference
Immunodeficiencies Affecting Cellular and Humoral Immunity (Including CID with Associated or Syndromic Features)				
SCID	***IL2RG* (X-SCID)** ***RAG1***	**XL** **AR**	**Gut microbiota and fecal metabolite composition can be differentiated into pre- and post-HSCT groups.** **Gut microbiota of X-SCID patients changes to more resemble those of healthy children after successful gene therapy.**	[1][2] [3]
Wiskott-Aldrich syndrome	***WAS***	**XL**	**Reduced fecal microbial community richness and diversity in WAS patients compared to age-matched healthy controls.** **Among WAS children, those with IBD and those who failed to express WASP, presented with more severe microbial dysbiosis.**	[4]
Predominantly antibody deficiencies				

Disease	Genetic Defect	Inheritance	Main Findings	Reference
Immunodeficiencies Affecting Cellular and Humoral Immunity (Including CID with Associated or Syndromic Features)				
CVID	Multiple genetic defects	Variable	In CVID patients with immune dysregulation, reduced microbial alpha diversity correlates with increased levels of LPS, soluble CD14 and CD25, and reduced IgA serum levels. IgG from healthy subjects targets the microbiota of CVID patients much less effectively than the microbiota of healthy subjects. Elevated concentrations of the gut microbiota-dependent metabolite TMAO is associated with systemic inflammation and increased gut microbial abundance of *Gammaproteobacteria* in CVID patients A single broad-spectrum antibiotic (rifaximin) does not modify microbial translocation, immune cell activation, and immune dysregulation	[5] [6] [7] [8]
sIgAD	Unknown	Unknown	Adequate IgM and/or IgG induction in sIgAD may protect from endotoxemia, while this compensatory response is lacking in CVID.	[9][10]
Other IEI				
CGD	*CYBB, CYBA, CYBC1,* NCF1, NCF2, NCF4	XL AR	Gut microbiota of patients with different genetic defects has distinct alterations; moreover, patients with the same gene defect who differ for the presence or absence of GI involvement display different microbial communities.	[11]
XIAP deficiency	*XIAP*	XL		
TTC7A deficiency	*TTC7A*	AR		
IL-10 receptor deficiency	*IL10RA*	AR	The degree of gut dysbiosis (calculated based on the relative abundance of five taxa at the order level: *Lactobacillales, Micrococcales, Veillonellaceae, Clostridiales, and Selenomonadales*) appears to be directly associated to disease severity.	[12]
IPEX	*FOXP3*	XL	First report on the effect of FMT before HSCT in a child with IPEX	[13]

AR, autosomal recessive; AD, autosomal dominant; CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; FMT, fecal microbiota transplantation; HSTC, hematopoietic stem cell transplantation; IEI, inborn errors of immunity; IL-10, interleukin-10; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; LPS, lipopolysaccharide; sIgAD, selective IgA deficiency; SCID, severe combined immunodeficiency; TMAO, trimethylamine N-oxide. TTC7A, Tetratricopeptide Repeat Domain 7A; XIAP, X-linked inhibitor of apoptosis; XL, X-linked.

2. Conclusions

Host immunity and microbiota interplay is a crucial symbiotic and dynamic relationship. Several lines of investigation have highlighted how the immune system plays a central role in shaping the composition of the microbiota. At the same time, resident commensals provide signals that induce normal immune system development and instruct the ensuing immune responses. As we continue to shed light on the cellular and molecular mechanisms of currently known IEI and describe new ones, additional insights into the interactions between host-immunity, the microbiome, and gut function are emerging. The advent of -omic technologies, including shotgun metagenomics, metatranscriptomics, and metabolomics, has created a high volume of complex data to more deeply characterize phenotypes of both the microbiome and the host, and in turn unveil potential pathobiological mechanisms as well as therapeutic strategies. Although only a few studies of the microbiome in patients with IEI have been performed to date, the interest in this field is rapidly growing. By studying IEI, we can understand which cells and molecular mechanisms are fundamental for immune function at barrier sites as well as non-redundant pathways required for intestinal colonization by commensal microbes. One common characteristic of the IEI microbiome is the decrease in microbial species typically associated with health. Intestinal commensals directly antagonize the proliferation of pathogenic bacteria and favor immune mechanisms to suppress competing microbes, overall activating responses that maintain epithelial barrier integrity. Alterations of the gut microbiota-host interactions may underlie aberrant immune responses in IEI. However, independent and ideally larger and longitudinal studies are required to confirm these findings. Considering the potential confounding factors such as sex, age, diet, treatment, geographical location, socioeconomic features, and gastrointestinal symptoms is particularly difficult, yet fundamental, in studies aiming at discriminating genetic factors from environmental influences. Of note, IEI patients frequently require antimicrobial

therapy 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. Finally, given the reported relationship between gut microbiota composition and IEI, the use of therapeutic intervention to correct intestinal dysbiosis may hold promise. The manipulation of the gut microbiota, through pharmacologic modification/decontamination or FMT, may shape the microbiota composition, depleting pathogenic bacteria and/or reconstituting missing health microbes, overall favoring intestinal homeostasis. However, to benefit for the gut microbiota as a target and an instrument of therapy, it is fundamental to fully understand the gut microbiota-host interactions in patients with IEI and clearly demonstrate the efficacy and safety of these procedures.

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