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REVIEW

A Comprehensive Review of IL-10 and IL-10 Receptor Deficiencies: From Basic Science to Clinical Bedside

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Abstract

Interleukin 10 (IL-10) is a potent anti-inflammatory cytokine. IL-10 receptor (IL-10R) consists of two chains of ligand-binding IL-10RA and two subunits of IL-10RB. IL-10 and IL-10R play important role in maintaining immune homeostasis in the gastrointestinal tract. Mutations in the *IL10*, *IL10R* cause spontaneous colitis in mice model and very early onset inflammatory bowel disease (VEOIBD) in human. Patients who have disease onset before 6 years of age are defined as VEOIBD. *IL10* and *IL10* receptor defect are classified as one type of monogenic inborn errors of immunity (IEI). IL-10 signalling defects demonstrate a Mendelian inheritance pattern with complete penetrance of intestinal inflammation. Patients develop symptoms during infancy and have more severe phenotype than polygenic inflammatory bowel disease (IBD). Here, we review the recent advances in the genetic mechanism, population dynamics and innate and adaptive immune dysregulation and interactions of gut microbiota regarding IL-10 signalling defects. The understanding of the pathogenesis has informed therapeutic strategies including haematopoietic stem cell transplant and novel biologics such as interleukin 1 receptor antagonist. Optimised transplant regimen and decreased risk of graft versus host disease with gut immunomodulation with vedolizumab might be used to improve transplant outcomes. More recently, gene therapy and gene editing have become treatment options for a range of IEIs, however evidence for IL-10 signalling defects is limited to in vitro and in vivo models. Beyond the Mendelian disorders, IL-10 signalling and neutralizing autoantibodies against IL-10 is relevant to the pathogenesis of polygenic IBD.

Keywords Interleukin 10 · Interleukin 10 receptor · IL-10 signalling · Genetic defect · Review

Introduction

Interleukin 10 (IL-10) and its receptor are important in maintaining immune haemostasis in the gastrointestinal tract [1]. IL-10 is a potent anti-inflammatory cytokine which inhibits proinflammatory and co-stimulatory function in the innate and adaptive immune cells [2]. IL-10R is a heterotetramer consisting of two chains of ligand-binding IL-10RA and two subunits of IL-10RB [3]. The IL-10 signalling defects lead to deficient signal transducer and activator of transcription 3 (STAT3) phosphorylation on stimulation with IL-10 and increased production of tumour necrosis factor α and other proinflammatory cytokines [4]. Mice deficient in *IL10* or the *IL10R* develop chronic spontaneous colitis [5, 6].

Very early onset inflammatory bowel disease (VEOIBD) are patients who have disease onset before six years of age [7]. VEOIBD patients present with more severe and refractory phenotype than late-onset paediatric IBD (diagnosed between 6 and 16 years of age) [8]. Mutations in *IL10* and its receptors were identified in VEOIBD patients presenting with early-onset IBD, peri-anal abscesses and enteric fistulas, which was initially reported in 2009 [4].

Here, we provide a clinical and scientific review of the IL-10 signalling defects, focusing on genotypes, mechanisms and pathways, current therapies and future research associated with human IBD and implications for targeted therapy.

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Genetic Mechanisms and Population Dynamics

There have been around 300 patients reported with IL-10 signalling since the first description in 2009 [9]. Based on the large cohort study and a systematic review, most patients have *IL10RA* defects, followed by mutation in *IL10RB* and *IL10* [9, 10]. The most common variants in *IL10RA* are homozygous missense mutation or heterozygous missense mutations. Among all mutations, the *IL10RA* c.C301T (p.R101W and c.G537A (p.T179T) mutations are the most common mutations [10]. Both mutations are significantly more prevalent among patients from East Asia than among those of other regions [10]. There is no significant difference in disease onset time, perianal lesion involvement, or mortality rate among patients with *IL10*, *IL10RA* or *IL10RB* deficiencies, however, B-cell lymphoma is more commonly associated with *IL10RB* deficiency [9, 10].

When proband clinical exome sequencing only identified one heterozygous pathogenic variant in the *IL10RA* among a VEOIBD patients, trio genome sequencing showed an additional novel deletion spanning exon 1 (c.-149_67 + 117del) [11]. Subsequently, another five patients were found to have this 333 bp deletion spanning exon 1 of the *IL10RA* gene and another missense mutation, and one patient has homozygous mutation of the 333 bp deletion in *IL10RA* [11]. Later another study also reported four VEOIBD patients with the same deletion [12]. Because the 333 bp deletion cannot be captured by the routine analysis of clinical exome sequencing or whole exome sequencing, these patients had delayed genetic diagnosis. More recently, Shi et al. reported the first case of apparent homozygous mutations in *IL10RA* [13]. Using a combination of whole-exome sequencing, comparative genomic hybridization and SNP array, a paternal uniparental diploidy (c.301 C > T/11q12.3-11q25del) [upd (11) pat] on chromosome 11 was identified in a VEOIBD patient. Together with earlier studies, it is essential to apply additional sequencing methods such as genome sequencing when initial genetic analysis is inconclusive, as exon-based approaches are limited to detect deletions or duplications. Notably, large deletions have also been identified in *IL10RB*, while no phenotypic differences are shown in patients with large deletions and other types of mutations [9].

There is also a geographic accumulation of confirmed pathogenic *IL10RA* variants in East Asia [14]. Possible explanation of high frequency of a rare genetic disease in a certain population includes founder effect, genetic drift or selective advantage [15]. Based on the geospatial association analysis between pathogenic *IL10RA* variants and human pathogen distribution worldwide, *Schistosomiasis japonicum* might be the cause of long-term pathogen-mediated natural selection pressure for these variants in East Asia [14]. Interestingly, a recent study identified a founder effect of *IL10RB* W40X mutation using low-pass whole genome sequencing data and haplotype analysis surrounding *IL10RB* in several members of the pedigree from an indigenous group living in a remote region of Ecuador [16]. This is consistent with another study, which reported a copy number variation with founder effect in *IL10RB* in the Portuguese kindreds [17]. Collectively, these results highlight the necessity of advanced sequencing strategies to provide accurate genetic diagnosis and to understand the population genetics and the evolutionary consequences of these mutations.

Pathway and Mechanism

Defective Anti-Inflammatory Function in IL-10 Signalling Defects

When IL-10 binds to the its receptors, IL-10RA and IL-10RB, Janus tyrosine kinases, JAK1 and Tyk2 are activated, resulting in the phosphorylation of STAT3 (signal transducer and activator of transcription 3) and the induction of STAT3-dependent genes, including *SOCS-3* [18]. Expression of *SOCS-3* inhibits various inflammatory cytokines including TNF, IL-6, and IL-1β [19]. In the context of IL-10 signalling defects, peripheral blood mononuclear cells (PBMCs) from patients could not induce IL-10-mediated STAT3 phosphorylation or inhibition of TNF-induced pro-inflammatory cytokine secretion [4]. The abrogated IL-10 signaling leads to hyperinflammation, which is consistent with the extensive intestinal inflammation, severe perianal diseases presented in patients with IL-10 signalling defects [4, 20].

Phenocopy of IL-10 Signalling Defects Due to Anti-IL-10 Autoantibodies

High titre neutralizing autoantibodies against IL-10 was identified in infantile-onset IBD patients without pathogenic mutations detected on genetic sequencing [21]. Functional assay showed unresponsiveness of patient's PBMCs to IL-10, while normal response was confirmed upon isolation by density gradient centrifugation and thorough washing of the PBMCs. Therefore, phenocopy of the IL-10 signalling defects were suggested due to the high titer of auto-antibodies to IL-10 [21]. One patient had disease onset at 3 months with severe IBD phenotype and another patient presented with moderate pancolitis from 4.5 years of age. Interestingly, both patients had high titre of anti-IL-10 autoantibodies which blocked the IL-10-dependent downregulation of the TNF-α response to LPS [21]. B cell-depleting therapy

Table 1 Comparison of characteristics of patients with IL-10 signalling defects and IBD patients with anti-IL-10 autoantibodies

	IL-10 signalling defects	IBD Patients with anti-IL-10 autoantibodies
Onset age	Neonatal onset in 70%,almost all cases before 2 years of age	3 months, 4 years;adult-onset cases reported
Genetic findings	Mutations in *IL10*, *IL10RA* or *IL10RB*	Absence of pathogenic mutations of VEOIBD
Phenotype	Severe colitis and multiple perianal diseases, B-cell lymphoma more common in *IL10RB* deficiency	Moderate to severe pancolitis, without perianal disease; adult patients with UC
Functional assay	Absence of pSTAT3 on stimulation with IL-10 and increased production of TNF-α	Absence of pSTAT3 on stimulation with IL-10, but normal response after density gradient centrifugation and thorough washing of PBMCs
Treatment	Curative: HSCT; Enterostomy for severe perianal disease or inflammation; Bridge therapy: anakinra	Severe case: Rituximab + IVIG; Mild case: steroids, azathioprine and infliximab

HSCT Haematopoietic stem-cell transplantation, *IVIG* intravenous immunoglobulin, *pSTAT3* phosphorylation of signal transducer andactivator of transcription 3, *PBMC* peripheral blood mononuclear cells, *TNF-α* tumour necrosis factor α, *UC* ulcerative colitis

with rituximab combined with intravenous immunoglobulin led to clinical response in one patient, while the other patient with milder course did not require B cell-depleting therapy [21]. Previously, higher levels of anti-IL-10 antibodies were found in 17% of the adult patients with CD [22]. Together with earlier findings, further studies are required to investigate the role of anti-IL10 autoantibodies in paediatric and adult IBD, which phenocopy the monogenic IBD caused by IL-10 signalling defects. These studies show that pathogenesis observed in the rare monogenic diseases might be generalisable to the non-genetic diseases which affect a larger populations and provide further implications for developing targeted therapy in selected patients. The comparisons of charateristics of patients with IL-10 signalling defects and IBD patients with anti-IL-10 autoantibodies are shown in Table 1.

Innate Immune Dysregulation in IL-10 Signalling Defects

Both innate and adaptive immune dysregulation have been observed in IL-10 signalling defects (Fig. 1). Cytokines produced by innate and adaptive immune cells contribute to the pathogenesis of IBD [23]. Increased inflammatory cytokine IL-1β is found in active IBD and IL-1β is involved in the colitis development and Th17 associated response in

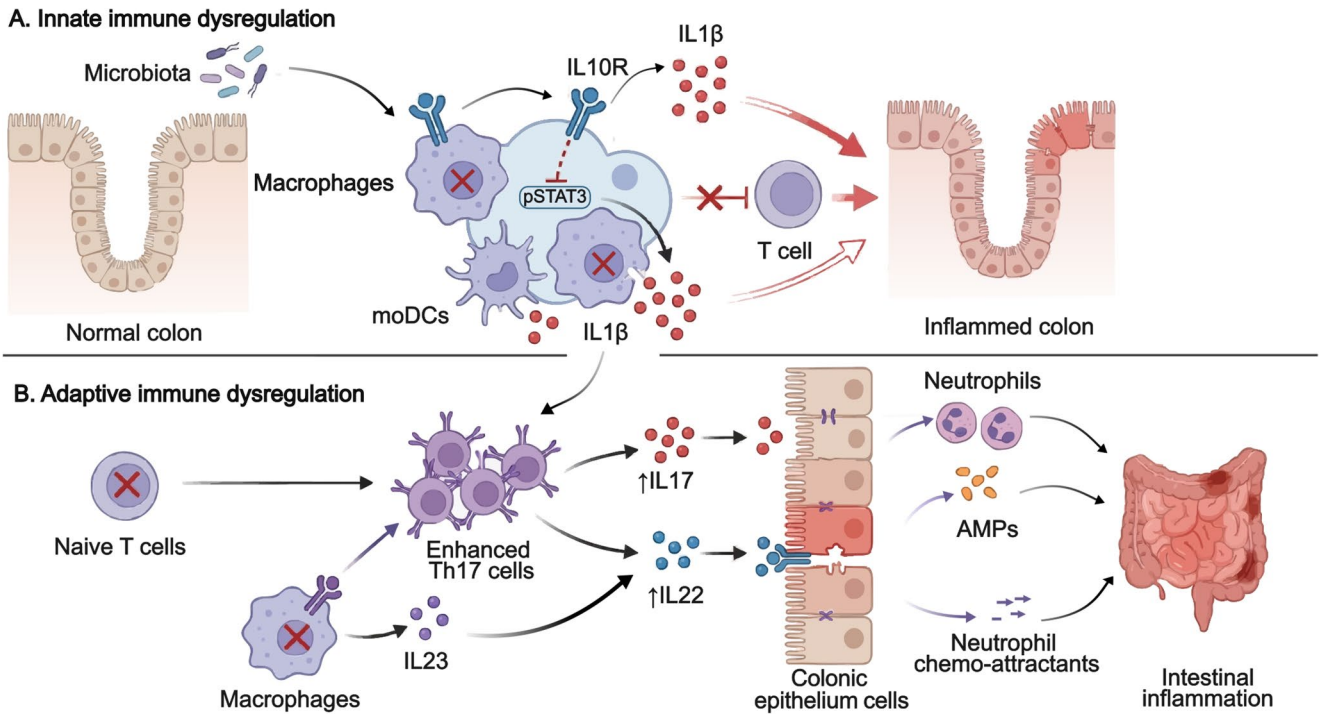

Fig. 1 Innate and adaptive immune dysregulation in IL-10 signalling defects. Both innate and adaptive immune dysregulation are associated with the pathogenesis of IL-10 signalling defects. The defective macrophages and monocyte-derived dendritic cells (moDC) produce increased IL1β, which lead to intestinal inflammation. IL10R-deficient T naive cells exhibit increased proliferation and enhanced Th17 response. The defective macrophages produce IL23, which recruits TH17 cells and induces secretion of IL22 to cause intestinal inflammation. AMP: antimicrobial peptide, moDC: monocyte-derived dendritic cells.

the intestine [24]. Stimulation of murine and human *IL10R*-deficient macrophages by LPS + ATP led to increased IL-1β production which was not suppressed by IL-10 pre-treatment [25]. Furthermore, LPS stimulation alone increased IL-1β secretion via noncanonical, caspase 8-dependent activation of the inflammasome in the human *IL10R*-deficient macrophages [25]. Notably, there is signiciant differences in innate immune regulation between the human and murine *IL10R*-deficient macrophages. Macrophages derived from patients are capable of producing IL-1β upon LPS activation without the secondary inflammasome activatin trigger (for example ATP) [25]. Overall, this finding suggested that blocking IL-1 in patients with IL-10 signalling defects may be beneficial, which has been supported by successful treatment outcomes with anakinra in two patients. Cellular metabolism in macrophages have shown profound changes in the metabolic profiles during macrophage activation and it is essential for regulating inflammation and tissue repair [26]. Macrophages accumulate damaged mitochondria in *Il10*$^{-/-}$ mice and *IL10R*-deficient patients, which resulted in dysregulated activation of the NLRP3 inflammasome and production of IL-1β [27]. Inhibition of ROS or mTOR signalling by antioxidants or rapamycin, can suppress the IL-1β secretion in the monocyte-derived macrophages from IL10R-deficient patients [27]. Consequently, targeting the mTORC1 pathway in macrophages could be beneficial for treatment or prevention of IBD. Interestingly, time-series experiments using *Il10rb*$^{-/-}$ mice showed that intestinal inflammation and macrophage dysfunction started during the third week of life, coinciding with weaning and the associated diversification of the intestinal microbiota [28]. As a large cohort study on patient with IL-10 signalling defects showed that 70.3% (97 of 138) had onset of disease during neonatal period and only 2.2% (3 of 138) had onset after 1 year old, understanding the timing and development of colitis using murine model would be essential [10]. Taken together, these results indicate that IL-10R-mediated regulation of macrophage function during the early postnatal period might be the critical time window leading to the development colitis.

Another study revealed that IL-10 signalling in monocyte-derived dendritic cells (moDCs) is crucial for controlling IFNγ-secreting CD4 + T cells [29]. IL-10 signalling defects significantly increased IL-1β release by moDCs [29]. Subsequently, a subgroup of paediatric IBD patients having higher IL-1β expression in activated immune cells and affected intestinal tissue were identified, together with a subgroup of patients exhibited diminished IL-10 responsiveness [29]. Notably, this finding corroborates with another study, for which IL-10R expression and IL10-induced pSTAT3 were decreased in monocytes from patients with Crohn's Disease (CD) [30]. Collectively, these results highlighted the important role of IL-10 signalling in the moDCs and monocytes and IL-1β as a potential classifier for IBD patients.

Adaptive Immune Dysregulation in IL-10 Signalling Defects

IL10R-dependent signals have been proved to be critical for the regulatory and effector CD4 + T-cell function in mice [31]. *IL10R*-deficient T naive cells exhibit increased proliferation and enhanced Th17 response [32]. Increased innate immune production of IL-1β in *IL10R* deficiency leads to enhanced production of IL-17 A [32]. Concurrently, *IL10RA*-deficient gut macrophages produce IL-23, which recruits pathogenic Th17 cells and induces secretion of IL-22 in the Cx3cr1^{cre}:Il10ra$^{fl/fl}$ mice model [33, 34]. Subsequently, colonic ECs respond to IL-22 exposure by expression of antimicrobial peptide (AMPs) and neutrophil chemo-attractants that drive a proinflammatory epithelial cell response model [34]. Although IL-22 is generally considered to be protective for intestinal inflammation and might be involved in wound healing [35]. The protection from colitis observed in *IL22*-deficient Cx3cr1^{cre}:Il10ra$^{fl/fl}$ mice indicates the pro-inflammatory role of IL-22 in the context of IL-10 signalling defects. In contrast, anakinra treatment led to mucosal healing associated with increased frequency of IL-22-producing lymphocytes in the lamina propria of the terminal ileum in a patient with *IL10RA* mutations [36].

Beyond dysregulated cytokine production, impaired IL-10 signalling also affects the adaptive immune compartment at the level of antigen receptor diversity. Next generation sequencing of the T and B cell receptor repertories demonstrates the adaptive immune function in many immune-mediated disorders, including UC, juvenile idiopathic arthritis and Wiskott-Aldrich syndrome [37–39]. Both the T and B cell receptor repertoires were skewed in patients with IL-10 signalling defects and are characterized by enhanced clonality, and alterations in repertoire features especially in T cells [40]. These findings are consistent with the studies of IBD without underlying genetic defects and other chronic intestinal inflammation [41, 42].

Collectively, these results provide mechanistic insights into the adaptive immune dysregulation triggered by the IL-10 signalling defects. Targeting the key cytokines may be beneficial for suppressing intestinal inflammation and inducing mucosal healing in such patients.

Microbiota and in IL-10 Signalling Defects

There is a significant association between gut microbiota and IBD, for example, relative increase in Proteobacteria, mainly *E. coli*, was identified in CD patients [43]. Environmental factors might modify the variable expressivity,

progression, severity, and onset of some monogenic diseases, including Cystic fibrosis, Huntington disease [44]. Interestingly, germ free *IL10*-deficient mice did not develop colitis, which suggested that normal enteric bacteria are essential for the development of spontaneous colitis in IL-10 signalling defects [45]. .

The changes in diversity and composition in the gut microbiota of IL10-deficient mice during the onset and progression of colitis were initially described. Increase in *Proteobacteria* and *Escherichia coli* were reported in IL10-deficient mice [46]. Subsequently, the relative abundance of *Firmicutes* was significantly increased in patients with *IL10RA* defects compared to healthy controls [47]. Another study showed a significant decrease in the abundance and diversity of the gut microbiota among *IL10RA*-deficient patients compared to those with late-onset paediatric IBD and non-monogenic VEOIBD [48]. The author also identified genus *Bifidobacterium* as a potential diagnostic indicator for different groups of IBD [48]. Furthermore, association between microbiota and engraftment failure has also been examined in patients with *IL10RA* defects undergoing umbilical cord blood transplantation (UCBT). Patients achieved successful engraftment had a higher level of *Lautropia* genus that sustained throughout the UCBT and had significantly higher Shannon diversity values on the UCBT day [49].

Therapeutic Strategies

A wide range of classic IBD treatment have been tested in patients with IL-10 signalling defects. As the advanced understanding of the underlying pathogenesis, more targeted therapy has been considered (Fig. 2).

Immunomodulator

Classic medical therapies suppress the immune system, which helps control intestinal inflammation [50]. Many immunomodulators targeting various pathways, including methotrexate [20], azathioprine [51], ciclosporin [51], tacrolimus [20] and mercaptopurine [52] have been tried in patients with IL-10 signalling defects, but almost all have been proved to be ineffective. Thalidomide might be an alternative option for refractory paediatric IBD with significant remission and clinical improvement based on a narrative review of 14 studies involving 213 children including 16 cases with IL-10 signalling defects [53]. Thalidomide has been reported in several studies and most patients with

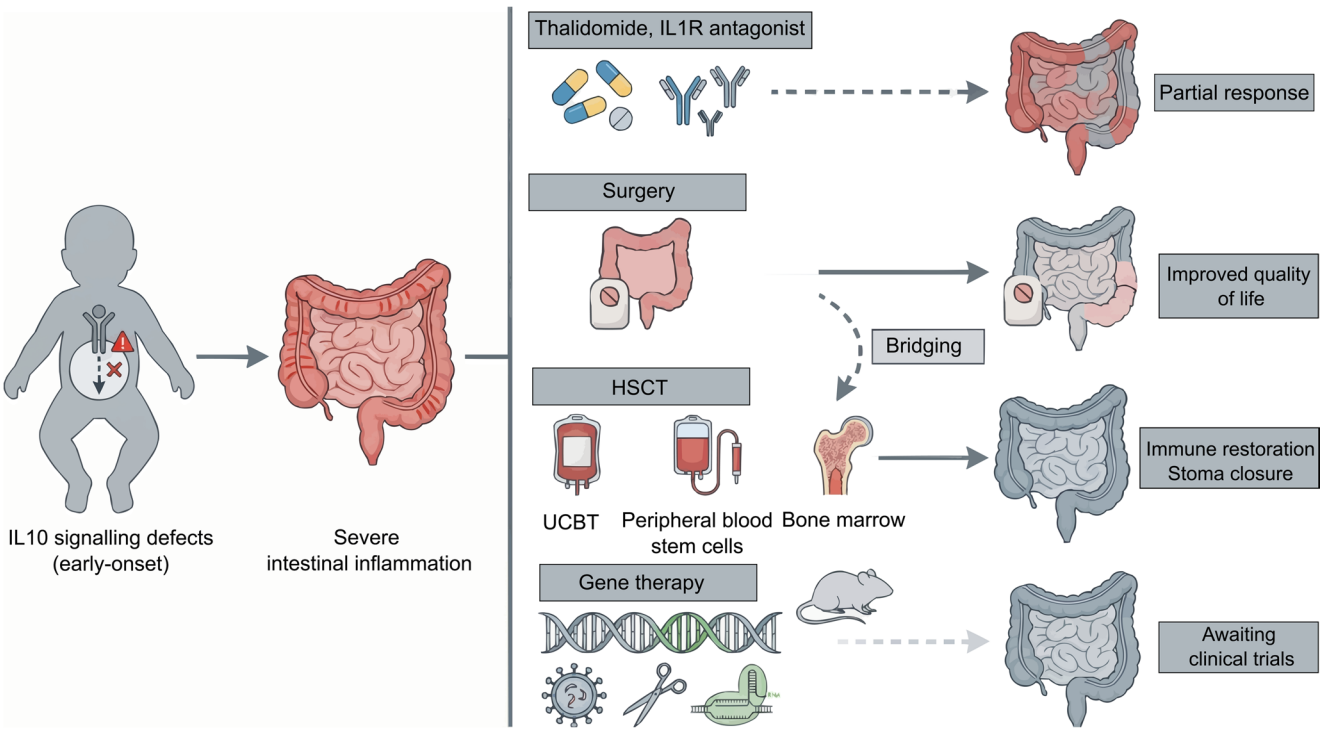

Fig. 2 Current and prospective treatment options for the IL-10 signalling defects. Current treatment options include immunomodulator, biologics, surgery and haematopoietic stem cell transplant. Thalidomide and interleukin 1 receptor antagonist might lead to partial response. Surgical intervention especially enterostomy is a bridging therapy which can significantly improve quality of life. HSCT can be curative to the patients and allows subsequent stoma closure. Gene therapy is only available in the murine model and further clinical trials are required. HSCT: haematopoietic stem cell transplant, IL1R: interleukin 1 receptor, IL10: interleukin 10, UCBT: umbilical cord blood transplant.

IL-10 signalling defects showed partial response to the treatment [20, 54–56]. A recent retrospective cohort study showed that thalidomide is effective and tolerable in children with VEOIBD, however, monogenic patients were excluded [57]. However, thalidomide is associated with multiple adverse effects including peripheral neuropathy, sedation and constipation [58], which have been reported in patients with IL-10 signalling defects [51, 55]. Veenbergen et al. showed that thalidomide decreased TNF-α derived from PBMC from one patient with *IL10RA* deficiency [54]. Thalidomide has many immunomodulatory properties, which can inhibit TNF, IFN-c, IL-12, block NF-kB activation and vascular endothelial growth factor [59, 60]. Compared to other immunosuppressives used in IBD, thalidomide shows broader immunomodulatory properties and is less pathway specific. This might explain the reason why patients with IL-10 signaling defects might have partial response with this medication instead of other traditional immunosuppressive therapeutics.

Biologics

Anti-TNF therapy, including infliximab and adalimumab have showed established efficacy in achieving steroid-free clinical remission in paediatric luminal CD and ulcerative colitis based on multicentre clinical trials [61–63]. *IL10R*-deficient PBMCs are unresponsive to IL-10 dependent negative feedback regulation and result in increased TNF-α upon co-stimulation with LPS and IL-10 [20]. However, infliximab or adalimumab are proven to be ineffective or only partially effective in patients with IL-10 signalling defects [20, 51, 64, 65]. The possible reason could be that an anti-TNF therapy in IBD is dependent on the intact macrophage IL-10 signalling [66]. The *Il10KO* mice is completely resistant to anti-TNF therapy and blocking the IL-10 signalling with anti-IL-10Rα diminishes the therapeutic efficacy of anti-TNF in the severe combined immunodeficient animal model [66].

As outlined in the previous section, increased production of IL-1β is key driver of the colitis in IL-10 signalling defect. There are several case reports describing successful use of IL-1 receptor antagonist anakinra as the bridging therapy to HSCT in patients with *IL10R* deficiencies (*IL10RA* deficiency, $n = 2$, *IL10RB* deficiency, $n = 2$) with duplicate cases excluded [25, 36, 52, 65, 67, 68]. Importantly, all these patients showed marked clinical, endoscopic, and histologic responses after 4–7 weeks of anakinra, while two of them showed limited response to other biologics including infliximab, adalimumab and vedolizumab. Li et al. suggested that response to anakinra in *IL10RB*-deficient patients might be less effective as IL-22-mediated epithelial repair requires *IL10RB*, and blocking inflammation alone cannot restore mucosal healing with defective *IL10RB* [36]. The most recent report described a patient with *IL10RB* deficiency, who showed partial response (partially controlled systematic inflammation and improved stool frequency) to anakinra following a failed HSCT [65]. This patient responded to canakinumab but still suffered from episodic flares of disease. These results highlight the emerging role of IL-1 blockade among patients with IL-10 signalling defects, as IL-1 inhibition is considered as useful bridge therapy, whereas other available biologics have shown limited benefit [67].

Surgery

Patients with IL-10 signalling defects had higher rates of requiring surgical interventions as well as the larger sample of VEOIBD [60]. More than half (52.5%) of the patients with IL-10 signalling defects had intestinal surgery based on a large cohort study [10]. The estimated risk of abdominal surgery among paediatric CD has been reported to be 20% and 9% in children with UC to receive colectomy [69, 70].

Most patients with IL10R deficiencies underwent selective enterostomy (27/46) or emergent enterostomy (19/46) because of intestinal perforation, severe obstruction or stenosis [55, 71]. End stomas, loop stomas, Bishop-Koop stomas and separate double-barrel stomas have been reported based on the extent of the intestinal lesions [71]. Notably, wound infections or dehiscence were common complications and required debridement and vacuum sealing drainage or reoperations [71]. Stomal-related and surgical incision related complications have been described in a prospective cohort study of IL10R deficient patients [72]. Univariate analysis showed that Weight-for-age Z-score, height-for-age Z-score, surgical method, C-reactive protein (CRP) and weighted Paediatric CD Activity Index score were significant risk factors of incision complications [72].

Importantly, the role of surgery in IL-10 signalling defects is different from those among IBD patients without genetic defects [73]. Surgery may be curative for paediatric UC but not CD patients [69]. Surgical intervention is unlikely curative to patients with IL-10 signalling defects, as recurrent active disease frequently develops despite multiple surgeries among these patients [25, 74]. Based on a ten-year follow up of *IL10R*-deficient patients undergoing enterostomy, 76% (35/46) of the patients had subsequent HSCT and 25 out of 35 were alive (71%); 76% (19/25) patients received stoma closure and others did not have the procedure due to short time frame since HSCT [73]. Stoma closure is only recommended after correction of the genetic defects to achieve favourable functional outcomes and quality of life [55, 75].

In addition, IL-10 signalling defects are strongly associated with severe and complex perianal diseases, including fissure, skin tag, abscess, perianal fistula, rectovaginal fistula and rectourethral fistula [10]. About 94.2% patients (131/139) with IL-10 signalling defects presented with multiple perianal lesions [10]. Severe perianal conditions are one of the indications for selective enterostomy [71]. Therefore, surgical intervention is crucial as a bridging therapy for IL-10 signalling defects and leads to better quality of life. Different and individualised approaches are required on surgical management for patients with IL-10 signalling defects who have more complex and distinct diseases compared with late-onset paediatric IBD.

Haematopoietic Stem-Cell Transplantation (HSCT)

The first successful case of *IL10RB* deficiency treated with HLA-matched sibling donor HSCT was reported by Glocker et al. in 2009 [4]. Since then, multiple cases of HSCT have been reported. Yanagi et al. reported the first case of *IL10RA* deficiency treated with UCBT [76] and Peng et al. described the first large cohort of nine cases with UCBT [77]. Source of HSCT includes cord blood, peripheral blood stem cells and bone marrow.

Strict gut decolonization was performed using colistin and total parenteral nutrition during the peri-transplantation [4, 20].Vedolizumab is effective in inducing remission in paediatric IBD although not being used in IL-10 signalling defects [78]. Vedolizumab targets locally to the GI tract and has been proved to be useful in the prevention of gut aGVHD after HSCT in adults and children [79]. There is a trend toward an increased risk of grade II-IV aGVHD in patients with monogenic IBD because peri-transplantation intestinal inflammation [80]. More recently, gut immunomodulation with vedolizumab prior to HSCT for the patients with monogenic IBD (IL10R deficiency, IPEX syndrome, SYK mutation) was reported first time, which showed good tolerance and associated with a lower rate of gut GVHD [81].

Based on a largest cohort of patients with IL-10 signalling defects (n = 102), the overall survival after transplantation (n = 73) was 64.2% (95% CI: 52.8–75.6), and among those without transplantation (n = 29) was 47.5% (95% CI: 14.8–80.2, P = 0.47) [55]. Despite the overall favourable outcome for patients undergoing HSCT, there are still reports of failed HSCT and death. Causes of death include sepsis due to engraftment failure, respiratory failure, multiple organ dysfunction syndrome and sinusoidal obstructive syndrome [76, 77, 82]. The HSCT outcomes are summarised in Table 2. Only studies published after 2020 were included. There are discrepancies in the number of patients and overall survival reported across studies, possibly reflecting differences in the incidence of these genetic defects in various populations.

This highlights the importance to identify risk factors associated with successful HSCT and better outcomes. The survival probability was higher in patients with pre-HSCT enterostomy, who had HSCT performed after 2 years of age without significant difference. Timeframe between disease onset and transplant, graft source, genotypes and thalidomide treatment were not significant risk factors associated with survival probability after HSCT [55]. Utilising biomarkers, another cohort study showed that serum IL6 and stool occult blood were independent prognostic risk factors of UCBT [82]. A Cox proportional hazards regression model with variables including stool occult blood, length- or height-for-age Z-score, medical history of sepsis, and cord blood total nucleated cells showed good discrimination ability to predict overall survival after UCBT [82].

Table 2 Summary of haematopoietic stem cell transplant outcomes among patients with IL10 signalling defects after 2020

Year	*N*	Donor type	OS	Follow up	Ref
2022	73	UCBT, MSD, MUD	64.2%	9.5 M	[54]
2024	80	UCBT	65.0%	29.4 M	[74]
2024	5	UCBT, BM	100%	45 M	[87]
2025	7	UCBT, MSD, MUD	80.0%	17.2 M	[88]
2025	4	NA	100%	36 M	[89]

BM bone marrow, *IL10* interleukin 10, *MUD* matched unrelated donor, *MSD* matched sibling donor, *M* moths, *N* number of patients, *NA* not available, *OS* overall survival, *Ref* reference, *UCBT* umbilical cord blood transplant

Gene editing and gene therapy

IL-10 signalling defects are classified as immune dysregulation with colitis according to the updated classification of inborn errors of immunity [83]. Besides these defects, there are other IEI also associated with IBD phenotype, including chronic granulomatous disease (CGD), XIAP deficiency, NEMO deficiency [83]. Compared to CGD, IL-10 signalling defects were reported later and with a smaller sample of affected patients. Table 3 shows the comparison of IL-10 signalling defects and CGD. Gene therapy has been widely tested and proved to be effective in other IEIs, for example, Wiskott-Aldrich syndrome [84], adenosine deaminase deficiency [85] and CGD [86].

Using CRISPR/Cas9 genome editing, a humanized $Il10ra^{R104W/R104W}$ mouse model was generated, which developed spontaneous colitis and the phenotype can be ameliorated by bone marrow transplantation [87]. Subsequently, both gene editing and lentiviral vector-based gene therapy can restore the anti-inflammatory responses in iPSC-derived macrophages from patients with *IL10RB* deficiencies. In the $Il10rb^{-/-}$ mouse model, haematopoietic stem cell gene therapy can restore defective IL-10 signalling in

Table 3 Comparison of monogenic inflammatory bowel disease due to IL-10 signalling defects and inborn errors of immunity associated inflammatory bowel disease

	IL-10 signalling defects	Chronic granumotaous disease
Genetic defects	AR: IL10, IL10RA, IL10RB	X-linked: CYBBAR: NCF1, NCF2
Pathogenesis	Defective phosphylation of STAT3 and unsuppressed intestinal inflammation	Defective NADPH oxidase function in phagocytes
IBD phenotype	100%	50%
Extra-intestinal	Skin folliculitis, recurrent infections, lymphoma	Invasive infections, autoimmunity
HSCT	Initial report as well as HSCT reported in 2009[8] OS: 64–100%	Disease initially reported in 1957[87] and first HSCT reported in 1977[88] OS: 84–90%
Gene therapy	Not available	Lentiviral gene therapy[78], Gene editing[89]
Clinical trial	No	NCT06325709, NCT06559176, NCT05207657

AR autosomal recessive, *HSCT* haematopoietic stem cell transplant, *IL-10* interleukin 10, *NADPH* nicotinamide adenine dinucleotide phosphate, *OS* overall survival, *STAT3* Signal transducer and activator of transcription 3

macrophages and significantly reduce colitis symptoms [88]. So far, there is no gene therapy clinical trial for the IL-10 signalling defects. Findings from both in vitro and in vivo mouse models support the feasibility of genetic correction of using gene editing or gene therapy. These preclinical findings might provide evidence to further investigate the effect and safety of gene editing and gene therapy in clinical trials. Given the limited evidence for gene therapy in IL-10 signalling defects, most available clinical trial data were derived from studies of other monogenic defects. In the first-in-human studies, the use of autologous CD34 + haematopoietic stem and progenitor cell-based lentiviral gene therapy in 9 patients showed good efficacy among 6 patients without no new CGD-related infections, while two patients died within 3 months of treatment due to pre-existing comorbidities [86]. More recently, prime editing of CD34 + cells were reported in two patients with autosomal recessive p47phox-deficient CGD who achieved restored NADPH oxidase activity [89]. Because CGD is a well-studied disease with a larger patient population, it attracts more research than the IL-10 signalling defects. There are challenges of delivering gene therapies for patients with ultra-rare disease [90].

Gene therapy has been considered as an alternative to HSCT for the IEI. Although HSCT is curative to IL-10 signalling defects, there are still concerns regarding the graft donor compatibility, rejection and GVHD. Therefore, further studies and gene therapy clinical trials may be beneficial for patients with IL-10 signalling defects as the other IEIs, and this can be challenged by the risk of oncogenesis as well as regulatory and financial obstacles [91, 92].

Conclusion

Since the first description in 2009, IL-10 signalling defects has become the important feature of VEOIBD due to monogenic defects. Unsuppressed intestinal inflammation resulting from the defective IL-10 signalling demonstrates complex interplay between innate and adaptive immune dysregulation and interactions with gut microbiota. Despited the promising use of biologics including anakinra and canakinumab, such patients remain at high risk of surgical intervention and transplant associated risks, as transplant is the only approved curative treatment. Further targeted therapy, for example gene therapy is awaited. Improved understanding of IL-10 signalling defects will provide implications for broader pathogenesis in the polygenic IBD.

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Authors' Contributions J.X. and Z.Y. concepted, performed literature review, drafted the review and prepared figures. Z.Y. and Y.H. critically reviewed and revised the article. All authors have read and approved the article.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethics Approval and Consent to Participate Not applicable.

Competing Interests The authors declare no competing interests.

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