Inflammatory bowel diseases and primary immunodeficiency diseases

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1. Introduction

Most diseases are associated with imbalances between intrinsic genetic factors and extrinsic environmental factors. Whereas inflammatory diseases have mainly been considered consequences of heterogeneous environmental factors, recent advances in gene analysis have led to the identification of genetic components of inflammatory diseases. Among technology advances, genome-wide association studies (GWAS) of inflammatory diseases have revealed genetic loci that play central roles in pathological inflammation. Concomitantly, whole-exome and whole-genome sequencing studies have identified more than 300 genes that are causative for primary immunodeficiency diseases (PIDs) and some of these are genetic loci that have been associated with inflammatory diseases. Hence, inflammatory diseases such as inflammatory bowel disease (IBD), multiple sclerosis, rheumatoid arthritis, type 1 diabetes mellitus, and systemic lupus erythematosus may be related to PIDs. In this review, genetic interactions between IBD and PIDs are discussed.

2. Genes associated with IBD

IBD encompasses all inflammatory diseases that affect the gastrointestinal tract. Crohn’s disease (CD) and uncreative colitis (UC) are the major IBD and symptoms associated with gut inflammation include abdominal pain, fever, diarrhea, rectal bleeding, anemia, and weight loss. Although patients with IBD cannot be fundamentally cured, the symptoms can be managed using anti-inflammatory steroids or immunosuppressant, or through dietary changes and surgery. CD and UC share several clinical features, but are distinguished by incidence patterns, disease localization, histopathology, and endoscopic features, and these differences may reflect underlying pathological mechanism [2,3]. The prevalence of IBD is highest in Europe and North America [4], but is rising in Japan due to increasing consumption of Westernized diets.

IBD is characterized by dysregulated immune responses to unknown environmental triggers, and it is thought to occur in genetically susceptible individuals. Twin studies revealed that coincidence of IBD is higher in monozygotic twins than in dizygotic twins, suggesting genetic contributor to IBD risk [5]. Linkage analyses also linked chromosome 16 with CD [6], and the candidate gene was finally identified as NOD2, which plays an important role in the recognition of bacterial peptidoglycans, hence, immune responses [7,8]. Yet NOD2 did not play a significant role in the pathogenesis of CD in a Japanese population [9]. GWAS showed that the genes IL23R and ATG16L1 are related to CD [10,11]. IL23R encodes a receptor protein that is presented on cell membranes of many different immune types, whereas ATG16L1 encodes a protein
that is involved in autophagy. Meta-analyses revealed a total number of 163 IBD loci [12], and previously described associations of these with innate immune responses, activation of adaptive immune responses, and regulation of adaptive immune responses, indicate these pathways in the pathogenesis of IBD (Table 1). Immunochip is a low-cost contemporary GWAS chip, and includes 70% (113 of 163) of the identified IBD loci. In further meta-analysis and trans-ancestry studies, more than 200 IBD-associated loci were identified (Figure 1). Some of these IBD-associated loci include genes that are involved in PIDs, including ADA, CD40, TAP1, TAP2, NBN, BLM, DNMT3B, STAT3, SP110, and STAT5B.

### 3. Monogenic IBD

Pediatric-onset IBD is that observed in patients of less than 17 years of age and is further classified into subgroups based on age at diagnosis (Table 2) [13,14]. Patients with early-onset IBD (EOIBD) and very early-onset IBD (VEOIBD) are diagnosed before 10 and 6 years of age, respectively. Diagnoses in infants of less than 2 years and less than 28 days are considered infantile and neonatal IBD, respectively. Many patients with VEOIBD have low response rates to conventional anti-inflammatory and immunomodulatory therapy and may have monogenic defects. Monogenic IBD has been documented in patients with a diverse spectrum of genetic disorders. Hence, it is important to distinguish between patients with monogenic IBD and conventional IBD, because the former require treatment with allogeneic hematopoietic stem cell transplantation (HSCT). Moreover, monogenic defects were shown to alter intestinal immune homeostasis through several mechanisms, and other single gene defects have been associated with hyperinflammation or autoinflammation, and disruption of T- and B-cell selection and activation.

### 4. Diagnosis of monogenic IBD

As described above, the early diagnosis of VEOIBD is critical for the design of treatment strategies. Monogenic IBD is primarily suspected in young patients (Figure 2) [15]. In addition to early onset, diagnoses of monogenic IBD are supported by diagnosis of IBD in multiple family members, consanguinity, autoimmunity, failure to thrive, conventional treatment failure, endocrine abnormality, recurrent infectious or unexplained fevers, severe perianal disease, macrophage activation syndrome and hemophagocytic lymphohistiocytosis, obstruction and atresia of the intestine, skin lesions and dental and hair abnormalities, and the presence of malignancies.

IBD is typically diagnosed from endoscopic and histopathological observations. The histopathology of IBD is classified as CD, UC, or IBD unclassified, and the latter is frequently observed in patients with VEOIBD, especially those with monogenic IBD. Various functional and genetic tests are required to confirm monogenic IBD in patients with VEOID (Figure 3). These include analyses of

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**Table 1. Pathways implicated in IBD pathogenesis.**

| Pathway implicated | Pathway genes in IBD-associated loci |
|--------------------|-------------------------------------|
| Innate immune response | CDH1, ERBBF1, GNA12, HRNF4A, ITLN1, MUC19, NKX2-3, PLA2G2E, PTGERA, REL, STAT3 |
| Innate mucosal defence | CARD9, FCGR2A, IL1RAP, ITLN1, NOD2, REL, SLCT1A1 |
| Autophagy | ATG16L1, CUL2, DAP, IRGM, LRRK2, NOD2, PARK7 |
| Apoptosis/necroptosis | DAP, FASLG, MST1, PUS10, THADA |
| Activation of adaptive immune response | CCR6, IL12B, IL21, IL23R, JAK2, STAT3, STAT4, TYK2 |
| IL23R response pathway | NFKB1, REL, TNFAIP3, TNIP1 |
| Aminopeptidases | ERAP1, ERAP2 |
| IL-2 and IL-21 T-cell activation | IL2, IL21, IL2RA |
| Regulation of adaptive immune response | AHR, CCR6, IL2, IL23R, IRF4, JAK2, ROAC, STAT3, TNFSF15, TYK2 |
| TH17 cell differentiation | ICOSLG, IFNG, IL12B, IL2, IL21, IL23R, IL2RA, IL7R, NDFIP1, PIM3, PRDM1, TAPAP, TNFRSF9, TNFRSF8 |
| T-cell activation | BACH2, IKZF1, IL5, IL7R, IRF5 |
| B-cell activation | |

**Table 2. Subgroups of pediatric IBD based on age.**

| Group | Age range |
|-------|-----------|
| Pediatric-onset IBD | <17 years |
| EOIBD | <10 years |
| VEOIBD | <6 years |
| Infantile-onset IBD | <2 years |
| Neonatal IBD | <28 days |

EOIBD: early onset IBD; VEOIBD: very early onset IBD.
neutrophil-mediated oxidative bursts using nitroblue tetrazolium tests or flow cytometry-based assays, measurements of IgG, IgA, IgM, and IgE, and flow cytometric assays of lymphocyte subsets, such as CD3⁺ T, CD4⁺ T, CD8⁺ T, CD19/CD20⁺ B, and CD16/CD56⁺ natural killer (NK) cells. All types of chronic granulomatous disease can be diagnosed using assays of the neutrophil oxidative burst. Patients with common variable immunodeficiency and agammaglobulinemia show reduced levels of all class immunoglobulins. Patients with hyper IgM syndrome generally have normal to elevated levels of IgM but reduced levels of IgG and IgA. Elevated levels of IgE and/or eosinophilia are also observed in patients with monogenic defects in FOXP3, IL2RA, IKBKG, WAS, or DOCK8 genes. Whereas all patients with severe combined immunodeficiency (SCID) lack T cells, the associated impact on B and NK cells vary between genetic defects. For example, X-linked agammaglobulinemia is associated with reduced numbers of circulating B cells. Moreover, FOXP3 expression in CD4⁺CD25⁺ T cells is reduced in a proportion of patients with immune dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX) syndrome [16,17]. XIAP expression is decreased in lymphocytes and monocytes of some patients with XIAP deficiency (Figure 4(a)) [17,18], and muramyl dipeptide signaling is selectively defective in patients with XIAP deficiency (Figure 4(b)) [19]. IL-10 receptor deficiency can also be detected using assays that determine whether exogenous IL-10 suppresses lipopolysaccharide-induced cytokine production in peripheral blood mononuclear cells [20,21]. Following functional screening of these deficiencies, candidate genes are generally sequenced to confirm the suspected genetic condition.

Candidate genes for monogenic IBD have recently become more numerous, but exhaustive sequencing of these is costly and time-consuming. Because of the greatly reduced costs of next-generation sequencing, multiplex gene sequencing may be cost-effective, and can be used to detect causative genes. We previously identified PID-associated genes in 35 Japanese patients with pediatric-onset IBD [22], and 27 of these had VEOIBD. In this study, 55 genes that have been associated with PID and/or IBD were selected for targeted gene panel analysis (Table 3). Gene defects were the identified

### YOUNG AGE MATTERS MOST

**Young age** onset in particular under 2 years of age

**Multiple family members and consanguinity**

**Autoimmunity**

**Thriving failure**

**Treatment with conventional medication fails**

**Endocrine concerns**

**Recurrent infections**

**Severe perianal disease**

**Macrophage activation syndrome/HLH**

**Obstruction and atresia of intestine**

**Skin lesions, dental and hair abnormalities**

**Tumors**

*Figure 2.* When should we suspect monogenic IBD? HLH: hemophagocytic lymphohistiocytosis.

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**Figure 3.** Diagnostic approach for VEOIBD. CBC: complete blood count; LPS: lipopolysaccharide; PBMC: peripheral blood mononuclear cell; CGD: chronic granulomatous disease; CVID: common variable immunodeficiency; SCID: severe combined immunodeficiency; IPEX: immune dysregulation, polyendocrinopathy, enteropathy, X-linked. The figure was modified from reference [15].
in 5 of the 35 patients (14.3%), and these included IL10RA in two patients, XIAP in two patients, and CYBB in one patient. Another group also suggested that targeted sequencing of a panel of genes is a fast and effective way to identify monogenic IBD [23].

Whole-exome sequencing (WES) is a genomic technique for sequencing all protein-coding genes in a genome, and these comprise 1% of the human genome. WES is a powerful tool for detecting genetic variants even in patients with atypical phenotypes. Previous WES studies identified XIAP [24], IL10RA [25,26], G6PC3 [27], MEFV [28], LRBA [29], FOXP3 [30], and TTC7A [31] as causative genes in patients with VEOIBD. WES can be also used to identify hypomorphic gene defects, these were shown in ZAP70, RAG2, IL2RG, LIG4, ADA, DCLRE1C, CD3G, and TTC7A for atypical SCID patients with associated IBD [32,33].

5. Novel monogenic IBD

Recent advances in genetic analyses including WES and whole-genome sequencing have allowed identification of novel mutations even in single patients. Below, I describe novel monogenic IBD types that were identified recently.

5.1. TRIM22

In a previous WES study, mutations in the tripartite motif containing 22 (TRIM22) gene were identified in three patients with VEOIBD [34]. TRIM22 is a RING finger E3 ubiquitin ligase that is expressed in intestinal cells and macrophages [35], and exhibits antiviral activity and activate nuclear factor-kB (NF-κB) signaling [36]. Because all three VEOIBD patients had distinct granulomatous colitis and severe perianal disease, it was concluded that the TRIM22-NOD2 network functions as a key antiviral and mycobacterial regulator.

5.2. NPC1

Niemann-Pick type C (NPC) is a neurodegenerative lysosomal storage disorder that is associated with defects in lysosomal calcium homeostasis and lipid
trafficking, and is caused by mutations in \textit{NPC1} and \textit{NPC2} genes [37]. Although patients with NPC1 often present with IBD, the associated functional mechanisms remain unclear. Nonetheless, mutation in \textit{NPC1} led to defects in autophagosome functions and abolished NOD2-mediated autophagy of bacteria [38]. Similar functional defects were observed in CD patients associated with NOD2 variants and XIAP deficiency. Taken together, these observations suggest that antibacterial autophagy that is initiated by the NOD2-RIPI2-XIAP pathway is a key defect in patients with granulomatous intestinal inflammation.

5.3. \textbf{NOX1}

In a study using whole-genome sequencing analyses, a patient with UC-like VEOIBD was shown to carry a novel hemizygous mutation in the \textit{NOX1} gene [39], and subsequent WES analyses identified other pediatric IBD patients with rare \textit{NOX1} variants. NOX1 is the catalytic subunit of superoxide-generating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex 1, and comprises NOX1, p22\textsubscript{phox}, NOXA1, NOXO1, and Rac1-GTP protein subunits [40]. NOX1 is a close structural homolog of the NADPH oxidase complex 2 component NOX2 (gp91\textsubscript{phox}, CYBB) and in phagocytes, NADPH complex 2 is responsible for the microbicial respiratory burst. NOX1 is located in membranes of intestinal epithelial cells [41] and was shown to constitutively generate high levels of reactive oxygen species (ROS) in the crypt lumen. A missense mutation abrogated ROS production by NOX1, suggesting that NOX1 variants change brush border ROS levels within colonic crypts at the interface between the epithelium and luminal microbes.

5.4. \textbf{TGFB1}

Transforming growth factor (TGF)-\(b\)1 (encoded by \textit{TGFB1}) is the prototypic member of the TGF-\(b\) family, which comprises proteins that have been widely associated with embryogenesis, development, and tissue homeostasis [42]. Dysfunctional TGF-\(b\)1 signaling is implicated in several human diseases, including cancer, cardiovascular disease, fibrosis, atherosclerosis, and various developmental disorders. In contrast, heterozygous gain-of-function mutations in \textit{TGFB1} cause Camurati-Engelmann disease, which is characterized by osteosclerotic lesions in long bones and the skull [43]. Biallelic loss-of-function mutations in \textit{TGFB1} were also identified in patients with severe IBD and central nervous system (CNS) diseases such as epilepsy, brain atrophy, and posterior leukoencephalopathy [44]. This study shows that TGF-\(b\)1 plays critical roles in the development and homeostasis of intestinal immunity and the CNS.

6. Treatment of IBD

Patients with IBD are currently treated with anti-inflammatory drugs and are encouraged to modify their diet. Surgery is rarely considered and is only performed in severe cases. Conventional drugs for IBD include prednisolone, methylprednisolone, budesonide, 5-aminosalicylic acid, 6-mercaptopurine, and methotrexate (Table 4). Treatment-resistant patients can subsequently be treated with infliximab and adalimumab, which are TNF-\(\alpha\) pathway blockade. Alternatively, IL-10R-deficient mice develop spontaneous colitis, and patients with mutations in \textit{IL10R} develop VEOIBD. These losses of IL-10 signaling lead to intestinal inflammation through increased production of IL-1 by innate immune cells, leading to CD4\(^+\) T cell activation [45]. Therefore, agents that block IL-1 signaling might be used to treat patients with IL10R deficiency-related IBD.

IL-18 blockade may also be effective in some patients with monogenic IBD. Patients with XIAP deficiency often have sustained levels of serum IL-18 during convalescence [46]. The patients are frequently associated with hemophagocytic lymphohistiocytosis (HLH), and HLH susceptibility in XIAP deficiency has been associated with high serum IL-18 levels. Gain-of-function mutations in NLRC4 which activates the inflammasome, result in recurrent macrophage activation syndrome (MAS) with early-onset enterocolitis (NLRC4-MAS) [47,48]. Patients with NLRC4-MAS have extraordinarily high serum IL-18 levels. In accordance, recombinant human IL-18 binding protein (rhIL-18BP) had dramatically favorable effects in a refractory patient with NLRC4-MAS [49]. Patients with XIAP deficiency may be successfully treated with rhIL-18BP.

IL-10 and IL-10 receptor-deficient patients have been cured following allogeneic HSCT [20,21]. Patients with XIAP deficiency and IPEX syndrome were also successfully treated with allogeneic HSCT [50–52], suggesting that colonoscopic findings could be improved and monogenic IBD could be cured.

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\textbf{Table 4. Treatment of IBD.} \\
\hline
\textbf{Monogenic IBD} & \textbf{Polygenic IBD} \\
\hline
\textbf{Mendelian inheritance} & \textbf{Crohn’s disease and ulcerative colitis} \\
\textbf{Anakinra} (anti-IL-1R antagonist) & Prednisolone \\
\textbf{IL-18 target therapy} & Methylprednisolone \\
Budesonide & 5-aminosalicylic acid (Mesalazine) \\
Azathioprine & 6-mercaptopurine \\
Methotrexate & Methotrexate \\
Infliximab & Adalimumab \\
Adalimumab & \\
\textbf{Allogeneic HSCT} & \textbf{Autologous HSCT?} \\
\textbf{HSCT: hematopoietic stem cell transplantation.} & \\
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using allogeneic HSCT (Figure 5), although transplantation-related morbidities have been observed and remain a risk.

Published case reports suggest that HSCT may also be of benefit to some patients with CD. Accordingly, a randomized clinical trial of HSCT (n = 23) vs. control (n = 22) was conducted with refractory CD patients in Europe from 2007 to 2011 [53]. In this study, autologous HSCT did not significantly improve disease remission rate at 1 year, compared with conventional therapy. In contrast, a recent multicentre retrospective analysis showed that autologous HSCT is relatively safe and effectively controls treatment-resistant CD [54]. Further prospective randomized controlled trials of autologous HSCT vs. the standard of care are warranted.

7. Conclusion

A proportion of patients with VEOIBD have monogenic IB and these patients are frequently refractory to conventional treatment. Because patients with monogenic IBD can be cured using allogeneic HSCT, accurate genetic diagnoses are required to determine prognoses and to prescribe appropriate treatment. Further studies of monogenic IBD may also improve the understanding of the more complicated pathogenesis of polygenic IBD.

Disclosure statement

No potential conflict of interest was reported by the author.

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