World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i17.4846

World J Gastroenterol 2014 May 7; 20(17): 4846-4856
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (3): Inflammatory bowel disease

Inflammatory bowel disease and celiac disease: Overlaps and differences

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Supported by Grants from "Fondo de Investigaciones Sanitarias", PI11/00614; and "Fundación Eugenio Rodríguez Pascual"
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Received: September 27, 2013 Revised: November 20, 2013
Accepted: January 14, 2014
Published online: May 7, 2014

Abstract

Recent findings demonstrate the common genetic basis for many immune-mediated diseases, and consequently, the partially shared pathogenesis. We collected these findings and reviewed the extension of these overlaps to other disease characteristics. Two autoimmune diseases were selected that also share the specific target organ, the bowel. The etiology and immunopathogenesis of both conditions characterized by chronic intestinal inflammation, inflammatory bowel disease (IBD) and celiac disease (CeD), are not completely understood. Both are complex diseases with genetics and environment contributing to dysregulation of innate and adaptive immune responses, leading to chronic inflammation and disease. CeD constitutes a particular disease because the main environmental and genetic triggers are largely known. IBD comprises two main clinical forms, Crohn's disease and ulcerative colitis, which most likely involve a complex interplay between some components of the commensal microbiota and other environmental factors in their origin. These multifactorial diseases encompass a broad spectrum of clinical phenotypes and ages of onset, although the clinical presentation often differs depending on childhood or adult onset, with greater heterogeneity commonly observed in adults.

Key words: Disease susceptibility; Gene-environment interaction; Immune system; Inflammation; Microbiota; Inflammatory bowel disease

Core tip: Inflammatory bowel disease and celiac disease are two immune-mediated diseases characterized by chronic intestinal inflammation. Recent findings demonstrate shared genetics and functional pathways. We reviewed the extension of these overlaps to other disease features and suggest future research approaches.

Pascual V, Dieli-Crimi R, López-Palacios N, Bodas A, Medrano LM, Núñez C. Inflammatory bowel disease and celiac disease: Overlaps and differences. *World J Gastroenterol* 2014; 20(17): 4846-4856 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i17/4846.htm DOI: http://dx.doi.

org/10.3748/wjg.v20.i17.4846

INTRODUCTION

The immune system is essential for defense self against external pathogens, and to maintain homeostasis. Dysregulation between those two processes contributes to development of immune-mediated diseases. These diseases represent an important cause of chronic illness, with a consequent high impact on public health. Different diseases can be found under this term, including autoimmune and inflammatory conditions. In these cases, it is common to find a specific organ affected, as occurs in inflammatory bowel disease (IBD) and celiac disease (CeD), both involving damage of the gastrointestinal tract. The gut is highly exposed to exogenous and endogenous antigens and controlled inflammation is a key process in maintaining homeostasis. Different factors can contribute to alter this equilibrium and to disrupt health status. Decades of research have focused on identifying those contributing factors and the reason why one specific disease develops. Recent findings demonstrate the extensive overlap in the genetic basis of immune-mediated diseases, including IBD and CeD.

The present review summarizes the current knowledge of different features related to the two major clinical forms of IBD, Crohn's disease (CD) and ulcerative colitis (UC), and CeD, paying special attention to the overlaps and differences between them. These two diseases share genetic risk factors, and it would be interesting to know whether this overlap also extend to other disease characteristics in order to gain knowledge about common pathogenic mechanisms and possible shared treatments.

CeD is one of the most frequent immune-mediated diseases. In Europe and the US the current prevalence of CeD is around 1 per 100 individuals[1,2] and a similar prevalence probably exists worldwide, although it has not been as extensively studied[3,4]. IBD shows a lower prevalence with values ranging from 26 to 199 per 100000 individuals in CD and from 37 to 246 per 100000 individuals in UC[5]. The prevalence of IBD is higher in developed countries and urban areas. A recent increase in the prevalence of both CeD and IBD has been described as a consequence of several factors[6-8]. In CeD these factors include the development of more effective diagnostic tools[9].

IBD affects both sexes similarly and the highest incidence is found between the second and the fourth decade of life. CeD seems to be more frequent in women[10], although this depends on the age at onset[11]. CeD can be diagnosed in individuals at any age, but it appears more frequently during childhood[12].

The prevalence of CeD in patients with IBD is not clear. There are several cases in the literature describing the coexistence of both diseases in the same family or even in the same patient[13-18]. However, some authors consider that this is an incidental association and the prevalence of CeD is similar between IBD patients and the general population[19]. In fact, CD and UC patients are not considered a risk group for routine CeD screening.

CLINICAL PRESENTATION

A wide spectrum of clinical symptoms characterizes IBD and CeD. In addition, differences in the clinical presentation can be found depending on the age at diagnosis.

IBD manifests during childhood or adolescence in at least 20% of patients. This presentation is commonly more severe and extensive than that observed in adult-onset disease[20]. In CD, involvement of the upper gastrointestinal tract is more frequently observed at early onset[21]. Bloody, mucous diarrhea is the almost universal hallmark of UC, although additional symptoms may be also present. The initial symptoms of CD are more subtle and varied, partly as a result of its diffuse and diverse anatomical location. The constellation of abdominal pain, diarrhea, poor appetite and weight loss constitutes the classical presentation of CD in all age groups, and is the mode of presentation in nearly 80% of children and adolescents (with or without extraintestinal manifestations). Abdominal pain is the most common single symptom at presentation[22,23].

In CeD, the presentation may be variable, but diarrhea, which may be acute or insidious in onset, is the most common presenting symptom in children. On the contrary, mild and nonspecific gastrointestinal symptoms are common in adults with CeD, with intermittent diarrhea, diffuse abdominal pain, dyspepsia, constipation, asthenia, flatulence, bloating or abdominal discomfort being the most frequently observed symptoms. In adults, iron-deficiency anemia without response to any appropriate treatment is a frequently observed sign[24,25].

Extraintestinal manifestations may be present in IBD and CeD. In IBD, most of the extraintestinal manifestations are shared by CD and UC. They may accompany intestinal symptoms or, less commonly, precede or overshadow them. These manifestations seem to be related to activity (relapse/remission) and location of the disease. Although children and adults may share extraintestinal manifestations, their frequency is usually different. Ocular lesions seem to be less common in young patients and a childhood-onset of IBD, particularly CD, may represent a specific risk factor for long-term morbidity from clinical osteoporosis[26].

In CeD, extraintestinal manifestations are usually a consequence of nutrient malabsorption and may coexist with digestive symptoms. It is currently accepted that extraintestinal signs and symptoms are common and may be the only presenting manifestation, mainly in adults[25,27].

Table 1 summarizes the main clinical features for IBD and CeD. Several overlapping characteristics can be observed. Diarrhea and abdominal pain are digestive symptoms commonly observed in both groups, but they also share several extraintestinal manifestations, as iron-deficiency anemia, short stature or osteoporosis. Some

Table 1 Main clinical features associated with inflammatory bowel disease and celiac disease

IBD	CeD
Intestinal mucosal involvement	Intestinal mucosal involvement
Clinical heterogeneity	Clinical heterogeneity
Depending on location and severity	Depending on degree of gluten sensitivity and amount of gluten ingested
Symptomatic (relapses/remission)	Commonly symptomatic (early onset)
	Mono or oligosymptomatic (late onset)
Digestive signs or symptoms	Digestive signs or symptoms
Diarrhea (± rectorrhagia)	Diarrhea
Abdominal pain (less predominant in UC)	Abdominal distension
	Abdominal pain
	Constipation
	Dyspepsia
	Recurrent vomiting
	Pyrosis and regurgitation
	Irritable bowel syndrome with diarrhea predominance
Extraintestinal manifestations	Extraintestinal manifestations
Refractory iron-deficiency anemia	Refractory iron-deficiency anemia
Short stature	Short stature
Poor appetite	Failure to thrive
Weight loss (less prevalent and extreme in UC)	Dermatitis herpetiformis
Sexual maturation delay	Vitamin B12 deficiency
Pneumopathies	Neurological symptoms
Psychological syndromes	Menstrual disturbances
Joints: arthritis and arthralgias (the most common in both CD and UC)	Bleeding diathesis (malabsorption of vitamin K)
Ocular: acute episcleritis, uveitis, orbital myositis	Paresthesia, cramps and tetany (hypocalcemia)
Skin: erythema nodosum, pyoderma gangrenosum	Hepatobiliary system: hypertransaminasemia
Hepatobiliary system: primary sclerosing cholangitis (less predominant in CD), autoimmune hepatitis (unusual)	Osteopenia, osteomalacia and osteoporosis
	Edema, ascites and anasarca (hypoproteinemia)
Renal system: ureteral obstruction, hydronephrosis, urinary stones	Hypopituitarism and adrenal insufficiency
Vascular system: thrombocytosis, hyperfibrinogenemia, elevated factor Ⅴ-Ⅶ, depression antithrombin Ⅲ	Recurrent mouth ulcers
Bone: osteoporosis (less predominant in UC)	
Severe complications	Severe complications
Malnutrition with weight loss and emaciation	(In refractory CeD or in patients who do not follow a GFD)
Fistulae	Collagenous CeD
Abscesses	Ulcerative jejunitis
Obstruction	T cell lymphomas
Perforation	
Dysplasia and colorectal cancer	

IBD: Inflammatory bowel disease; CeD: Celiac disease; UC: Ulcerative colitis; CD: Crohn's disease; GFD: Gluten-free diet.

differences are also observed. CeD patients can remain asymptomatic, in contrast with the symptomatic IBD patients.

The major complications of CeD, ulcerative jejunitis and intestinal lymphoma, cause more severe clinical manifestations that may resemble CD, such as acute and persistent abdominal pain, weight loss, signs of intestinal obstruction or gastrointestinal bleeding, fever or signs of marked malnutrition[28]. It has been suggested that complicated CeD should be considered in CD patients who do not respond to immunosuppressive or biological treatments[29].

SEROLOGY

As frequently observed in autoimmune diseases, CeD is characterized by the presence of autoantibodies, which are currently included in the definition and diagnostic guidelines for CeD[30]. Transglutaminase type 2 (TG2) is the major autoantigen in CeD and the target antigen for endomysial antibodies (EMA) and anti-TG2 antibodies. Therefore, those two antibodies are the most specific for CeD diagnosis. Although a high correlation exists between anti-TG2 and EMA antibodies, the highest specificity is observed for EMA, because anti-TG2 can be present in individuals with other conditions, including CD and UC. However, it is difficult to know the frequency of anti-TG2 antibodies in IBD patients because the studies developed with that aim have yielded different results, probably partially caused by the wide variety of commercial kits used[18,19,31-35].

On the contrary, the presence of specific antibodies is not a common feature in IBD. Two major groups of serological markers have been described in these patients: those against microbial antigens and autoantibodies. Their relevance for IBD diagnosis is not as strong as for CeD, but they are useful to differentiate CD from UC patients. Among the antibodies against microbial agents, those against *Saccharomyces cerevisiae* (ASCAs) are the most extensively studied and they are related to CD. These anti-

bodies have also been described in CeD patients but they disappear after taking a gluten-free diet (GFD), which is supposedly due to the association of ASCAs with inflammation of the small bowel, and therefore, questions their specificity for CD[36]. Regarding autoantibodies, antineutrophil cytoplasmic antibodies have a high prevalence in UC[37].

ETIOLOGY

The causes underlying the development of IBD and CeD have not been completely unraveled, but both diseases show a multifactorial origin with a complex genetic and environmental involvement.

Environment

In this regard, CeD is the best-understood immune-mediated disease because the main environmental factor involved is largely known. CeD is triggered by ingestion of dietary wheat gluten or analogous proteins present in other cereal grains, mainly rye and barley.

Although gluten intake is necessary to develop CeD, other environmental factors may play a role. Infections have been related to CeD development. Specifically, rotavirus[38] and hepatitis B and C virus infections have been observed in CeD patients[39]. A protector role for breastfeeding at the moment of gluten introduction has also been described[40].

Viruses have also been implicated in the origin of IBD. The hygiene hypothesis establishes that lack of early exposure to microbial agents due to severe hygienic conditions could increase the likelihood of developing autoimmune and allergic disorders, and it has been used to explain the rising prevalence of IBD observed in industrialized countries[41]. Although to a lesser extent, this hypothesis has also been proposed for CeD[42]. Recent genetic findings support a role of pathogens in IBD and CeD.

Other environmental factors contributing to IBD risk are smoking and appendectomy. The effect of cigarette smoking is opposite in both forms of IBD: beneficial in UC and harmful in CD[43,44]. For appendectomy, it seems that it reduces the risk of UC[45,46].

Vitamin D levels, diet, hormone use and stress have also been postulated as risk factors for one or both main forms of IBD, but they need to be further investigated[47].

The environmental influence in IBD pathogenesis seems to involve complex mechanisms because its role in disease risk may be modified by other factors such as sex, geographic region, or genetic background[47]. Moreover, environmental factors are probably influencing the natural history in addition to the origin of these diseases.

Microbiota

An altered microbiota composition seems to be a common phenomenon in intestinal inflammatory disorders. In IBD, an abnormal response to the normal commensal flora of the bowel is considered to cause the disease[48,49]. The role of the microbiota in the pathogenesis of IBD was first suggested by studies in mice, which showed a lack of experimental colitis in animals kept in a germ-free environment[50]. Since then, numerous works have been published in this field. Although no final conclusions can be drawn, it is clear that no single pathogen is associated with the disease, and quantitative besides qualitative changes in the microbiota influence disease development[51,52].

Microbiota alterations have also been related to CeD risk, again with quantitative and qualitative changes reported[53,54]. In CeD, an altered microbial diversity depending on the clinical presentation has been recently described, with marked differences between patients showing classical gastrointestinal symptoms and those with extraintestinal manifestations[55].

The influence of diet (including breastfeeding) and cigarette smoking or the increased risk of disease in children born by Cesarean section have been postulated to be mediated through changes in the microbiota. These changes have also been linked to the increasing incidence of IBD and CeD in recent decades.

Nowadays it is clearly accepted that the intestinal microflora differs between healthy individuals and those showing CeD or IBD. It has been claimed that those differences could be a consequence of the disease. Among other functions, commensal bacteria of the gut contribute to protection against external pathogens and participate in the maturation of the mucosal immune system, supporting their role in the etiology of these diseases. Recent genetic studies are also concordant with a causal role[56]. Nevertheless, a complex situation exists because the microbiome can be altered as a result of infection or pathological processes.

Genetics

The genetic contribution to disease risk differs between CeD and IBD. The highest values are observed for CeD (75% of concordance between monozygotic twins)[57], followed by CD (44%-50%) and UC (16%)[58].

Knowledge of the genetic basis of immune-mediated diseases has dramatically increased in recent years with the advent of genome-wide association studies (GWAS). These studies analyze hundreds of thousands of common [minor allele frequency (MAF) > 5%] genetic variants (single nucleotide polymorphisms, SNPs) across the human genome, looking for variants with a different frequency between individuals showing the disease and the general population. They need high numbers of affected and unaffected individuals that provide enough statistical power to find significant associations. Initially, GWAS included around 1000 individuals with each phenotype, but this number has been increased in recent GWAS. Moreover, follow-up of the nonsignificant most associated SNPs and meta-analysis of previously published largescale studies have also been performed. Additionally, cross-disease meta-analyses that combine data of previous GWAS have been performed to identify susceptibility loci common to different immune-mediated diseases. Looking for variants shared between CD and CeD, these

studies have identified four new shared loci[59]. New approaches to study the genetic basis of IBD and CeD include the Immunochip Project, also based on the presence of a common genetic basis for immune-mediated diseases but focused on deep replication and fine mapping[56,60]; and the recently published high-throughput exon-sequencing of 25 GWAS risk genes[61].

GWAS are not based on prior hypothesis determined by previously available information (*e.g.,* gene function, previous association studies, and animal models) and the studied SNPs are selected to cover a high proportion of gene variation across the genome. With this approach, unexpected genes have been identified as related to disease susceptibility. The newly identified genes point out functional pathways involved in particular phenotypes, some of them also previously unexpected.

IBD and CeD show both a complex genetic basis that is characterized by the presence of numerous common susceptibility factors contributing a small risk to disease susceptibility. In IBD, no factor seems either necessary or sufficient to develop the disease, as it is commonly observed in complex diseases. However, CeD constitutes a particular case. It is commonly accepted that the main genetic risk alleles, those coding the HLA-DQ2 or -DQ8 heterodimers, are necessary although not sufficient to develop CeD, because they are present in almost all CeD patients.

The influence of the HLA region in disease risk marks more differences between IBD and CeD. This region, located on 6p21, contains hundreds of genes with immunological functions and it is responsible for the strongest association signals observed in most immune-mediated diseases. However, HLA influence is different between IBD and CeD, and these two diseases are at opposite ends of the spectrum. HLA loci are the main genetic susceptibility factors for CeD and they are responsible for 40% of the genetic risk; in addition, their functional involvement in disease pathogenesis is well established. On the contrary, a weak and a weak-moderate association is found in CD and UC, respectively. Moreover, the HLA alleles associated with IBD are markers of still unknown HLA risk variants[62].

Additional to the HLA region, 163 loci have been associated with IBD risk: 110 common to CD and UC, 30 specific for CD and 23 for UC[56]. For most of the specific loci, the same direction of effect exists in the two forms of IBD and only two loci (*NOD2* and *PTPN22*) have shown significant opposite effects between CD and UC[56]. In CeD, 40 susceptibility loci have been described[60,61]. The number of associated SNPs is even higher, because one SNP does not always account for the risk overall attributed to one locus. The causal variant or even the genes responsible for the reported associations remain unknown for many of these regions. In CeD, the individual gene involved is known for half of the associated regions. In both diseases, independent effects of the associated variants have been reported, as well as correlation of genotypes for many SNPs with expression levels, and an important role of noncoding variants. This last observation has been recently underscored by the discovered negligible impact of rare variants (MAF < 5%) within exons[61], until now considered as potential relevant contributors to disease risk. The different number of variants associated with IBD and CeD is probably mirroring the different sample sizes used in the studies.

The large sample sizes required by GWAS have been achieved thanks to international collaborations, but this necessary effort may overlook genetic factors associated with specific populations. A new genetic region (22q13.2) has been recently associated with CD risk in a GWAS performed in a Southern European population[63]. This encourages us to study homogeneous groups of patients (in terms of ethnicity or clinical features) to look for new genetic susceptibility factors.

GWAS have found similar genes associated with IBD when considering childhood or adult onset[56], although the severe inflammation that mutations in interleukin (*IL*)-*10RB* cause in children suffering extreme phenotypes, identified through other kind of genetic studies, must be highlighted[64]. In CeD, studies considering the age of onset remain to be performed.

Seventy percent (113/163) of the IBD loci are shared with other complex diseases, and 12% (20) with CeD. The picture is different when the number of CeD risk regions is used as a reference; 50% of the CeD loci are shared with IBD. Independent of the real percentage, which is impossible to ascertain until scientific advances provide us with a full knowledge of the genetic basis of these diseases, the existence of a common genetic background is evident.

Despite the huge advance in the genetic basis of these chronic diseases, only 14% of the genetic variance is known in CD, 7.5% in UC, and approximately 50% in CeD. The highest values of CeD are due to the strong influence of the HLA, which accounts for 40% of the genetic variance.

IMMUNOPATHOLOGY

The model of immunopathogenesis for CeD has long been established. Dietary gluten induces innate and adaptive immune responses. The innate immune response is characterized by the gluten-induced production of IL-15, which acts on intraepithelial lymphocytes and licenses them to kill epithelial cells. This increases permeability and facilitates that gluten peptides pass through the impaired epithelial barrier into the lamina propria. In this compartment, TG2 induces deamidation of gluten-derived peptides, creating epitopes that bind efficiently to HLA-DQ2/DQ8 heterodimers on antigen-presenting cells, and thus elicits a T-cell response[65,66].

GWAS findings suggest four main processes underlying CeD: T-cell development in the thymus, innate immune detection of viral RNA, T and B cell co-stimulation (or co-inhibition) and cytokines, chemokines and their receptors. It seems now that a specific enrichment for genes involved in natural killer (NK) cell activation

and interferon γ production also exists. Thus, besides T cells, other cell types may have special relevance in the pathological process, as B cells, NK cells or neutrophils, but the previous model of pathogenesis remains valid and basically unchanged.

In IBD, the model of pathogenesis is based on the dysregulation of the normally controlled immune response to commensal bacteria, which could be precipitated by infection or by defects in the mucosal barrier. This involves infiltration of several cells of the immune system and chemokine and cytokine production, which in turn exacerbate the dysfunctional immune response and activate either T helper (Th)1 or Th2 cells in the gut mucosa, associated with CD and less conclusively with UC, respectively[67].

GWAS results have been crucial in advancing our understanding of IBD pathogenesis. Two major findings were the unsuspected role of autophagy and the implication of the Th17 immune response. The genes associated with CD and UC risk point to shared pathways involved in the pathogenesis of these two inflammatory conditions.

The genes shared between IBD and CeD are mainly related to the innate immune response against pathogens and to the activation of the immune system to produce inflammation, including T-cell differentiation and immune-cell signaling. Specific pathways like autophagy and Th17 response seem to be only involved in IBD. Autophagy is responsible for degradation of intracellular structures, but it is also important in removal and recognition of invasive pathogens. Its involvement in CD etiology was suggested after the association of *ATG16L1, LRRK2* and *IRGM* with CD risk. The implication of Th17 cells marks an important difference between IBD and CeD, because they have been associated with susceptibility to numerous immune-related diseases but not to CeD[60,68], which is still considered to be a Th1-mediated disease. Th17 cells are involved in defense against extracellular pathogens but they act as potent inducers of autoimmunity through their involvement in tissue inflammation and are probably linked to innate and adaptive responses[69]. *IL23R* was the first Th17 gene found in genetic association studies, but it was followed by numerous related loci: *IL22*, *IL17A*, *IL17F*, *TYK2*, *JAK2*, *CCR6* and *STAT3*.

In Figure 1, all the genes associated with IBD and CeD in large scale studies are shown. They have been grouped according to their predominant role in three major functions: innate immune response, adaptive immune response, and epithelial barrier function. All the genes with a different role or with still unknown function have been grouped as "others". The highest number of shared genes between IBD and CeD is observed for genes involved in adaptive immunity. The specific association with UC risk for most of the loci involved in barrier function is noteworthy.

Both CeD and IBD need an environmental stimulus that activates the immune system and leads to the pathological process. The amplification of the immune response involves release of cytokines, molecules involved in intracellular signaling, and transcription factors. GWAS have found many genes coding for products related to these processes. The initial stimulus to trigger the disease is different and it seems to be crucial in developing one or other disease, probably in combination with the genes specific for each disease.

Despite the scientific revolution prompted by GWAS, some issues still hamper a direct translation to disease pathogenesis: (1) in many regions, the genetic variant or even the gene responsible for the association remain to be identified; (2) many of the proteins detected are pleiotropic, with different possible roles and with still unknown functions; and (3) the immune responses, with complex networks of interactions that include specific molecules inducing up- or downregulation of the same functional pathway depending on the microenvironment.

TREATMENT

There is no single effective treatment for all IBD patients. Therefore, different treatments are used to manage the disease, often several of them in the same individual. Conventional immunosuppressive drugs, including azathioprine, mercaptopurine and methotrexate, are the initial treatment for IBD. When the immunosuppressive therapy losses efficacy or the patient continues with active disease, alternative biological therapies based on tumor necrosis factor (TNF)-α blockade are commonly used in IBD. In recent years, infliximab and adalimumab became standardized biological therapies in IBD. Infliximab is a chimeric monoclonal IgG1 anti-TNFα and it is indicated in refractory CD[70,71] and in acute severe UC[72]. Despite the high efficacy of infliximab, some patients do not respond to this treatment. An alternative therapy for these patients is adalimumab, an humanized TNF-α antibody, which decreases the risk of developing antibodies[73-75]; one of the causes of non-response to infliximab[76]. Based on the results of genetic studies, new biological therapies are currently being tested or are already in clinical use in IBD patients[77-80].

In CeD, treatment is a lifelong GFD. This is an effective and safe treatment, but there is a small group of patients who do not respond. Refractory CeD patients (RCeD) are defined as those showing persistent villous atrophy, crypt hyperplasia, and high levels of intraepithelial lymphocytes despite strict adherence to a GFD for > 12 mo[81,82]. There are two categories of RCeD, depending on the presence (type Ⅰ) or not (type Ⅱ) of aberrant intraepithelial T cells[83]. RCeD patients develop higher severe malnutrition combined with an increased risk for developing enteropathy-associated T-cell lymphoma[84]. Immunosuppressive therapy, similar to that used in IBD patients and based on azathioprine, cyclosporine or anti-TNF-α, is the current treatment for RCeD[84,85]. In the bad prognosis of RCeD, primarily type Ⅱ RCeD, chemotherapy shows moderate clinical, histological and hematological efficacy[86,87].

Figure 1 Immunopathology. Overlap between inflammatory bowel disease (IBD) [considering the two major forms Crohn's disease (CD) and ulcerative colitis (UC)] and celiac disease (CeD) for the loci identified by large scale genetic studies. Genes are grouped according to their participation in three main functional blocks: innate immunity, adaptive immunity, and intestinal barrier. All the genes with still unknown function are grouped as "others". Note that some genes can be found in more than one functional group.

New therapeutic approaches in CeD have increased in recent years. These therapies are focused on engineering gluten-free grains, decreasing the intestinal permeability by blockade of the epithelial zonulin receptor, inhibiting gluten peptide presentation by HLA-DQ2 antagonists, and inducing oral tolerance to gluten[88].

In both disorders, a delay in diagnosis or in proper treatment carries an increased risk of future complications. However, individuals with different autoimmune diseases can present similar symptoms, which sometimes makes it difficult to establish early diagnosis and treatment.

Reconstitution of the physiological flora remains an interesting therapeutic aim for both IBD and CeD.

FUTURE PERSPECTIVES

Despite the great advances in our understanding of IBD and CeD, we are still far from being able to anticipate who will develop some of these immune-mediated conditions. Ingestion of gluten and alterations in the commensal microbiota seem to be the main environmental triggers for CeD and IBD, respectively. However, it remains to be understood what is further needed to break the tolerance in specific individuals and develop disease.

Nevertheless, current advances related to the functional pathways involved in IBD are being useful in finding new drug targets. The shared molecular pathways between IBD and CeD open new possibilities for therapy in RCeD. With the identification of the causal variants in all the associated regions new clues about disease pathogenesis will be obtained and new treatment targets will appear.

Future epidemiological studies are necessary to gain knowledge about the genetic and environmental interactions that contribute to disease development. Better knowledge of the role of pathogens will also be useful to look for new therapies or prevent disease. Although numerous factors make it difficult to study the environmental contributing factors, some genes seem to point to specific triggers. Prospective as well as retrospective studies involving individuals with alterations in those genes could be performed, which aim to advance the role of those specific environmental triggers.

The multifactorial nature of the etiology of CeD and IBD likely hides great complexity due to the interplay among all the factors involved. The role of the microbiota seems to be influenced by interaction with external pathogens, but also by host genetic factors. More research is needed in this field, which will likely contribute to identifying where the missing heritability lies and a better understanding of the immunopathogenesis.

A broad range of symptoms characterize CeD and IBD. Subgroups of patients combining their clinical features with the presence of a similar genetic profile may help to establish more homogeneous groups to perform the next steps in research.

CONCLUSION

IBD and CeD are two immune-mediated disorders with a partially common genetic background. Overlaps between both disorders are also observed for other specific features; however, these conditions do not seem to be more strongly correlated with each other than with other immune-related disorders. The common clinical manifestations are probably a consequence of the target organ affected: the gut. Shared genetics originates the altered immune response and the inflammation characterizing both diseases. Nevertheless, comparison of these two diseases helps to understand what is specific for each disease and what is common. Common features may be useful to understand better the inflammatory processes and to look for new shared therapies.

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P- Reviewers: Ciaccio EJ, Rodrigo L **S- Editor**: Gou SX
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ISSN 1007-9327
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