Charlotte Hedin · John D. Rioux
Mauro D'Amato *Editors*

Molecular Genetics of Inflammatory Bowel Disease

Second Edition

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ISBN 978-3-030-28702-3 ISBN 978-3-030-28703-0 (eBook)
https://doi.org/10.1007/978-3-030-28703-0

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

In 2013, when the first edition of this book was published, the field of inflammatory bowel disease (IBD) was being galvanized by the ever-expanding range of new pathogenic pathways and potential molecular treatment targets discovered through genetic research. In the intervening 6 years, this knowledge base has been further enriched with new genes, pathways, epigenetic mechanisms, and a better understanding of the interaction between genotype and environment. Now, the web of intersecting and converging mechanisms is leading us away from classifying disease according to clinical phenotypes – Crohn's disease vs. ulcerative colitis, for example – toward a new molecular taxonomy of IBD. Such a classification has its roots in genetic surveys that are the result of multinational networks of large groups of scientists and clinicians, collaborating to deepen our knowledge of the genetic foundations of IBD. The genetic and molecular overlap between different chronic inflammatory conditions has brought the promise of a future, comprehensive molecular taxonomy spanning all chronic inflammatory diseases, which may facilitate highly personalized treatment. Scientists from a range of disciplines are engaging with IBD as the archetypal disease at the interface between the human immune system and the environment. Accumulating evidence suggests that the complex interactions between humans and the microenvironment that forms the gut may even be an arena for the indoctrination of the developing immune system cells. As such, the interface of the gut mucosa may have a role in defining an individual's lifelong immunological disposition. Understanding what happens when this interface is dysfunctional, such as in IBD, has the potential to illuminate its fundamental role in human health.

With eight entirely new chapters and additional updates and revisions, this book aims to cover the full spectrum of the contribution of genetics to the current understanding of IBD. Here, we review how the familial epidemiology of IBD makes evident what is known and what is unknown of the heritability of IBD. We introduce the utility of the available animal models of IBD for picking apart individual components of IBD pathogenesis. We detail the genes associated with IBD and examine the overlap with other chronic inflammatory disorders. The available methods for the genetic prediction of IBD risk are discussed, as well as the potential to implement

molecular profiling of IBD subtypes and therapy responses. The field of epigenetics gives insights into the mechanisms behind non-genetic but still heritable phenotypic traits. Epigenetic factors and posttranscriptional regulation of gene expression through, for example, micro-RNA, also underpin the influence of environment on the expression of the IBD risk genotype. Genetically driven variation in epithelial homeostasis alters gut barrier function and is causatively involved in IBD pathogenesis. Alterations in gut barrier function disturb the interaction between the gut microbiome and the human immune system, leading to imbalances on both sides. Ultimately, the cumulation of these insights, arising out of the newly identified genetic architecture of IBD, may provide the knowledge we need to better tailor therapy to the patient's specific genetic and molecular IBD signature. This book should serve as a guide for navigating the growing complexity of the molecular genetics of IBD.

Stockholm, Sweden — Charlotte Hedin
Montréal, QC, Canada — John D. Rioux
Clayton, VIC, Australia — Mauro D'Amato

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About the Editors

Charlotte Hedin, MD, PhD is a Specialist in Luminal Gastroenterology at the Karolinska University Hospital in Stockholm. She completed her PhD on Crohn's disease pathogenesis at King's College London and Queen Mary University of London. In 2017, she was awarded a UEG Rising Star Award for her research in IBD and, in 2018, the Karolina Prize for "Exemplary Patient Flow and Quality Work" at the Karolinska University Hospital. She holds a clinical postdoctorate from the Karolinska University Hospital. She is a Member of the Swedish Organisation for the Study of IBD (SOIBD)) and is Committee Member for the European Crohn's and Colitis Organisation (ECCO). In addition, she collaborates in international IBD research projects, including the GEM project. Dr. Hedin's research focusses on delineating pathogenic pathways in IBD through studying at-risk individuals (families of IBD patients) and defining the process of mucosal healing.

John D. Rioux, PhD is a Full Professor of Medicine at Université de Montréal (UdeM) and Senior Researcher at the Montreal Heart Institute (MHI) and holder of the Canada Research Chair in Genetics and Genomic Medicine. He is a Founding Member of multiple international consortia and currently co-leads the International IBD Genetics Consortium, is Chair of the Steering Committee of the NIDDK IBD Genetics Consortium and the Leader of the IBD Genomic Medicine (*iGenoMed*) Consortium. Dr. Rioux's research focuses on three main areas: (1) genetic studies to identify risk factors for common and rare diseases, (2) functional studies to understand how these genetic risk factors protect or predispose to disease, and (3) integrative human studies to identify predictive biomarkers of important clinical outcomes. His work has led to over 200 publications, cited over 30,000 times.

Mauro D'Amato, PhD is Professor of Genetics and Genomics and Head of the Gastrointestinal Genetics Unit at the School of Biological Sciences, Faculty of Science, Monash University, Melbourne, Australia. He conceived and coordinates the largest gene mapping effort in irritable bowel syndrome, the *bellygenes initiative* exploiting data from >800,000 individuals, has served in the Management Committee of several consortia including the International IBD Genetics Consortium, and is

Member of the European Microscopic Colitis Group. His team combines genomic, computational, and preclinical expertise to elucidate the pathogenetic mechanisms predisposing to inflammatory and functional gastrointestinal diseases. The druggable genome, nutrigenetics, and host (genome)-microbiota interactions are also new research lines within the group. His research has resulted in more than 150 publications and over 13,000 citations.

Part I
The Foundation of IBD Genetics: Human and Animal Models

A Primer on IBD: Phenotypes, Diagnosis, Treatment, and Clinical Challenges

Katherine Falloon and Mark Lazarev

Abstract Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract, most commonly divided into ulcerative colitis (UC) and Crohn's disease. We have seen an increase in incidence in IBD over the last few decades worldwide. UC and Crohn's disease have strong genetic underpinnings which have been steadily elucidated over the past 20 years. Additionally, there are number of environmental factors that have been recognized as triggers of disease, including dietary/microbiome and smoking. In this chapter, we lay out the primary phenotypes observed in Crohn's and UC. We next discuss the approach to diagnosis, which is generally multifactorial, including blood and stool testing, abdominal imaging, and colonoscopy with biopsy. Next, we summarize the treatment algorithms for both disease, including the pre- and post-biologic era. Greater concentration is given to the discussion of the anti-tumor necrosis factor (TNF) alpha, which to date has been the greatest game changer in IBD management. We also discuss the newer pharmacologic mechanisms of targeting the disease including lymphocyte adhesion blockers, anti-IL 12/23 inhibitors, and drugs that target the JAK/STAT pathway. Some of the newer agents in the pipeline are also briefly discussed. In the final section, we explore clinical correlates of the genetic findings to date. We delve into some of the key findings including the discovery of the *NOD2* risk gene, as well as the most up-to-date genome wide association studies (GWAS) findings. Through this we explore how these genetic findings correlate with specific disease phenotypes, and how the findings have helped choose targets for pharmacologic therapy.

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C. Hedin et al. (eds.), *Molecular Genetics of Inflammatory Bowel Disease*,
https://doi.org/10.1007/978-3-030-28703-0_1

Introduction

Inflammatory bowel disease encompasses a group of diseases that involve chronic, relapsing inflammation of the GI tract, divided into three main categories—ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis (IC). Another form of chronic colitis includes microscopic colitis (lymphocytic colitis, collagenous colitis); this group will not be covered in this review.

There appears to be a geographical pattern to IBD, with a North–South gradient both across the hemispheres and within individual countries [1, 2]. IBD predominates in the Western world, with rates highest in Europe and North America, where approximately 0.4% of the population lives with IBD [2, 3]. In the USA alone, this leads to a quarter million doctor visits, 30,000 hospitalizations, the loss of over a million workdays, and direct medical costs of over 4 billion annually [4–7]. Incidence of the disease around the world has either stabilized at a high rate or is increasing, suggesting the emergence of IBD as a global disease [8]. IBD is most prevalent among Caucasians, followed by African Americans, though incidence rates in Asian Americans and Hispanics are growing [9]. It is also more prevalent among the Ashkenazi Jewish population [10]. Peak onset is between 15 and 30 years, although the disease can begin at any age [8].

The pathogenesis of IBD is only partially understood. The prevailing theory posits that IBD is the result of an excessive inflammatory response to an environmental trigger (e.g., infection or medication) in a genetically predisposed individual. The "hygiene hypothesis" has been proposed to explain the geographic and demographic tendencies of IBD, with the thought that factors such as increased industrialization, sanitation, and quality of health care systems may help explain the increased risk of IBD in the Western world as well as in higher social strata [10–13]. In support of this hypothesis are studies demonstrating lower risk of IBD in larger or poorer families with lack of access to clean water as well as the increasing incidence rates among immigrants who move from low to high incidence regions, though understanding of the development of disease remains incomplete and further study is needed [14–16].

Genetics also play a role, with a positive family history still the greatest risk factor for IBD and a number of genes already implicated in development of the disease [10, 17]. Other factors of interest include diet, the microbiome, and smoking. There have been associations with specific dietary components or patterns and the development of IBD, but the quality of these studies is mixed and so it is challenging to draw any meaningful conclusions [10, 11, 18–20]. It is possible that dietary intake may be most important for the development of IBD in the way that it affects the gut microbiome. Numerous studies have demonstrated that dysbiosis is prominent in IBD, and when compared to healthy controls, patients with IBD have decreased numbers and reduced diversity of *Firmicutes* and *Bacteroides* [21, 22]. However, whether alterations in gut flora are the result of the disease or lead to it is still undetermined [18, 23–25]. Smoking worsens the course of CD but has been associated with more benign disease course in UC [26, 27]. The use of nonsteroidal anti-inflammatory drugs has also been shown to increase the frequency of flares in patients with IBD [28].

Clinical Manifestations and Phenotypes

The two main forms of IBD include UC and Crohn's disease. This distinction is important as the two diseases vary in both their pathogenesis and their treatment. UC is characterized by diffuse inflammation that is typically confined to the mucosa. It involves the rectum in the vast majority of cases and can extend in uninterrupted fashion to the rest of the large intestine but does not involve the small bowel [5]. Disease course is commonly characterized by the gradual onset of bloody diarrhea with urgency, tenesmus, and cramping abdominal pain [5, 29] There are various classification schemes for UC. The Montreal consensus classifies UC based on anatomic extent—ulcerative proctitis (E1), distal or left-sided UC (E2), and extensive UC involving the colon proximal to the splenic flexure (E3) [30]. Severity of disease can also be defined by the Mayo system, which takes into account factors such as stool pattern, rectal bleeding, and endoscopic findings [31]. Long-term complications may include medically refractory disease and rarely toxic megacolon, a dilation of the colon which left untreated could result in perforation.

Crohn's disease, on the other hand, involves transmural inflammation and can occur anywhere in the gastrointestinal tract [32]. Crohn's is most frequently classified according to disease location (terminal ileal or L1, colonic or L2, ileocolic or L3, isolated upper GI or L4) and behavior (non-stricturing and non-penetrating or B1, stricturing or B2, penetrating or B3) [32]. Fifty percent of patients present with ileocolonic disease, 80% will have ileitis, and 20% will have isolated colonic disease [33, 34]. Disease presentation is dependent on disease location but is typically characterized by diarrhea, abdominal pain, and weight loss. Involvement of the upper GI tract can lead to aphthous ulcers, nausea, and vomiting. Involvement of the small bowel can lead to malabsorption of bile acids, iron, vitamin B12, and fat soluble vitamins. Rectal bleeding is less typical except in those patients with Crohn's localized only to the colon. In CD, perianal disease is present in about 30–35% of patients [35–37]. Complications of perianal disease include perirectal abscesses, anorectal fistulas, and anal fistulas. Over time, left untreated, over 80% of patients with CD will develop some complication of disease, which includes strictures, fistulas, or abdominal abscesses [38].

Both Crohn's and UC can also have extra-intestinal manifestations. These include ocular complications (episcleritis, scleritis, uveitis), arthropathies and sacroiliitis, and dermatologic complications (erythema nodosum, pyoderma gangrenosum) [5, 32]. Primary sclerosing cholangitis (PSC) is more likely in patients with UC and is associated with a risk of chronic liver disease, and an increased risk of colorectal cancer [39, 40]. Anxiety and depression are also more common among patients with IBD, especially those with greater disease activity [41, 42].

Of note, approximately 5–10% of patients with IBD are unclassifiable and thus labeled as indeterminate colitis [43]. This is more common in children than in adults [44]. Other chronic colitides include microscopic colitis, in which the colon appears endoscopically normal but is characterized histologically by lymphocyte infiltrates (lymphocytic colitis), or a subepithelial collagen band (collagenous colitis) [45].

Diversion colitis can occur if part of the colon is excluded from the fecal stream [46]. Diverticular colitis, which is limited to portions of the colon with diverticula present, and pouchitis can occur in patients with UC who have undergone total proctocolectomy with ileal pouch-anal anastomosis [47]. Other diseases that can present similarly to IBD and may need to be considered based on clinical context include infections (infectious colitis, amebic colitis, schistosomiasis, intestinal TB), NSAID enteropathy, Behcet's, celiac disease, radiation colitis, ischemic colitis, intestinal lymphoma, eosinophilic enteritis, bile salt malabsorption, bacterial overgrowth, over-use or misuse of laxatives, irritable bowel syndrome (IBS), and colon cancer.

Diagnosis

The diagnosis of IBD is made based on clinical suspicion in combination with laboratory, radiologic, endoscopic, and histologic findings [48]. The clinical symptoms of IBD have been described above. Physical exam findings may include tachycardia, cachexia, abdominal distension, tenderness, rebound, or guarding, skin tags, fissures, or fistulas in the perianal region, or extra-intestinal manifestations such as aphthous ulcers or erythema nodosum. Patients in whom there is suspicion for IBD should be ruled out for infectious causes of symptoms via stool studies, including testing for C. difficile, which is also found at increased rates in patients with IBD [49, 50]. Pertinent blood work includes complete blood count (CBC) to look for anemia, ferritin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) to look for inflammation, and albumin and electrolytes to look for signs of malnutrition. Tissue transglutaminase IgA and quantitative IgA may also be performed to rule out celiac disease. Serologic testing includes perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) and anti-saccharomyces cerevisiae antibody (ASCA)—a positive p-ANCA and negative ASCA suggest UC while a negative p-ANCA and positive ASCA suggest CD—however, such testing is usually unnecessary if further endoscopic work-up is planned [29]. Fecal calprotectin and lactoferrin can be indicative of intestinal inflammation, though they are not specific for IBD associated intestinal inflammation.

From a radiologic perspective, plain abdominal films have little utility. Computerized tomography (CT) and magnetic resonance enterography (MRE) employ both a water-based oral contrast and intravenous IV contrast, and have become the standard for evaluating the small bowel for active disease, strictures, and fistulas. MRE has the added benefit of avoiding ionizing radiation. Barium studies are generally falling out of favor, largely secondary to lack of expertise in interpreting these studies, and the fact that they do not evaluate extraluminal regions (such as ruling out an abdominal abscess). Ultrasound is also emerging as an imaging modality that can be used to detect CD without exposing patients to radiation; however, its use has been limited as it is very operator dependent and