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Environment and Genes: What Is the Interaction?

Richard S. Blumberg

GI Division, Harvard Medical School Brigham and Women's Hospital, Boston, Mass., USA

Abstract

Inflammatory bowel disease (IBD) results from a continuum of complex interactions between a quartet of host-derived and external elements that involve various aspects of the intestinal microbiota, the immune system that is centered around the intestinal epithelial cell barrier, the genetic composition of the host and specific environmental factors. Recent studies into the complexity of these arrangements increasingly support the syndromic nature of this disorder and involve a wide range of interacting biologic pathways that affect innate immunity, adaptive immunity, endoplasmic reticulum stress and autophagy as well as metabolic pathways associated with cellular homeostasis. It is further likely that all of the aforementioned host factors including the microbiota, which is as much a part of ourselves as is any organ system, are under the influence of yet-to-be-understood environmental factors that predispose to and precipitate IBD. Notwithstanding the importance of genetic predisposition, these environmental influences are no doubt central to disease pathogenesis in light of the rapid emergence of IBD throughout the world and assumption of disease in migrating populations from low to high risk environments. It can thus be anticipated that environmental factors that modify the risk for development of IBD have the common attribute of affecting the relationship between the commensal microbiota and the immune system in a manner that intersects with the functionally relevant immuno-genetic pathways, and potentially modifies them through epigenetic effects, in a manner that are uniquely operative within a particular syndromic context of IBD and occur sequentially and in a reiterative fashion, perhaps beginning in early life.

Keywords

Inflammatory; Bowel; Disease; Environment; Genetics

It is increasingly recognized that inflammatory bowel disease (IBD) is a syndromic disorder. Moreover, our knowledge of the interaction between environmental influences and the genetic basis of these disorders has revealed a very complex relationship between these 2 central factors and the clinical manifestations of disease. Recent data suggest that IBD has continuous contribution of genetic influences that range from monogenic to allogenic to polygenic (fig. 1) [1]. In the former case, the onset of IBD in the first several years of life, so-called very early onset IBD (VEOIBD), has been shown by either whole exome or whole

Richard S. Blumberg, GI Division, Harvard Medical School, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115 (USA), ; Email: rblumberg@partners.org

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genome sequencing to be based on a monogenic defect [2]. In addition, approximately 10% of patients with these disorders exhibit a familial occurrence of IBD, either Crohn's disease (CD) or ulcerative colitis (UC), with both types of clinical phenotype often occurring in the same family. The latter is, as discussed below, consistent with the genetic overlap between these clinical manifestations. However, in the majority of cases, IBD has no familial association and therefore may be considered more polygenic, thus consequently possessing a more important contribution from environmental influences. At its most extreme, it still remains possible that IBD represents an undiagnosed infection that might be related to a variety of potential and increasingly described emerging infectious diseases. Thus, it might be considered that VEOIBD, familial IBD and sporadic IBD represent a continuum of disorders with variable degrees of genetic contribution. It is thus very clear that IBD exhibits a very complex relationship between genetic and environmental influences [3, 4].

Nature or Nurture: Which Is It?

One of the important interpretations of the extensive efforts performed over the past decade through genome-wide association studies (GWAS) is the implication and increasing support for the critical role played by environment. The basis for this statement is the large number of potential genes that have been implicated in the pathogenesis of this disorder, which represent at least 2% of the genome [5, 6]. To date, approximately 200 loci have been identified as being associated with both forms of IBD. Within these 200 loci, based upon single nucleotide polymorphism frequencies in IBD subjects versus controls, are approximately 1,500 potential associated genes [7, 8]. Moreover, GWAS has demonstrated that this genetic contribution only accounts for less than approximately 20% of the genetic variation, which is associated with disease risk. In that only a few genes contribute significantly to risk, such as *NOD2*, *ATG16L1*, *IL23R*, and that the remainder of defined and yet-to-be defined loci contribute progressively less to disease risk, it can be anticipated that IBD represents the complex interactions between potentially thousands of genes in a given host, especially those with sporadic IBD. In other words, in the large majority of IBD cases, the genetic contribution to disease may be similar to that associated with a variety of other complex traits, such as height or other autoimmune diseases [9]. This inferentially supports the critical role of environment.

IBD has long been considered to have an important relationship to environmental influences. One potential means by which environment may play a role is via the concept of the so-called 'hygiene hypothesis'. First described by Strachan [10] who reported early life exposures as critical for later life risk was later linked to improper infectious diseases by Bach [11]. In the latter instance, they noted the interesting inverse relationship between infectious disease and the increased incidences in a variety of complex immune-mediated diseases such as CD, multiple sclerosis, type I diabetes and asthma. More recently, Molodecky et al. [12] performed a systemic literature review of 262 studies published between 1950 and 2010 and noted that 75% of CD and 60% of UC studies exhibited an increasing incidence of disease. Moreover, they noticed the emergence of IBD in regions of the world that had previously not described such an association including in Asia, Africa, South America and the Middle East. They concluded that IBD is emerging as a global disease with increasing incidence and prevalence over time and in different regions of the

world. This supports the critical role played by environment in the pathogenesis of these disorders as genetics could not possibly have changed throughout the world in this short period of time. It is also interesting that approximately 70% of the genetic loci that are associated with IBD are also shared by a variety of autoimmune diseases [13]. This firstly suggests that the genetic underpinning of many autoimmune diseases is shared by IBD and is also consistent with its co-occurrence together with other autoimmune disorders. More to the point, this might suggest that a variety of complex autoimmune diseases share common environmental influences with IBD, which theoretically impinge upon a similar set of immuno-genetic pathways.

In this regard, an examination of the genetic studies suggests that the pathways that are associated with IBD are likely shared and involved in responses to environmental influences [3]. This is supported by the evidence that the genetic basis for IBD is shared with the genetic basis of responses to infectious diseases [5]. Infectious diseases are critical to IBD pathogenesis in that the entero-pathogens are a major environmental risk factor for IBD [14]. GWAS of leprosy, for example, has revealed similarities with CD [15]. The risk genes that are associated with both multi-bacillary and pauci-bacillary types of leprosy are shared with IBD. This suggests that genetic risk factors determine the phenotype of inflammation in leprosy and potentially IBD in response to a particular environmental influence. This is interesting given the wide variety of phenotypes associated with IBD suggesting that genetic risk factors may determine the phenotypes and the clinical manifestations of IBD, as well as in response to environmental factors. It is therefore interesting that IBD shares phenotypic manifestations with another mycobacterial infection, *Mycobacterium tuberculosis*. Together, these studies and the interpretation of the literature suggest that there is a complex influence of genetic and environmental factors in influencing the risk for developing and the clinical manifestations of IBD. At its core, the IBD is considered as a disorder that is derived from abnormal interactions between the commensal microbial milieu, the intestinal epithelial cell and the immune system [3]. This triad is critical in maintaining the barrier or interface between the outside and inside world. Within this concept, it might therefore be considered that genetic factors regulate each of these 3 parts of the triad as do the specific environmental factors, which influence these 3 central elements in very precise ways (fig. 2).

The Core Genetic Pathways That Are Associated with IBD and Their Relationship to the Environment

A parsimonious model is that IBD emerges from an inappropriate epithelial and immune system response to the commensal microbiota. As a corollary, it might be suggested that the epithelial cells and immune system are improperly regulated by the commensal microbiota. The commensal microbiota, in turn, is a part of ourselves and can arguably be considered as a self-regulated organ within the human body [16]. Conceptually, therefore, the commensal microbiota is not a component of the outside world but actually a central element of ourselves, which is under the influence of the environment (e.g., geographic upbringing, diet, antibiotics). Thus, in considering the genetic factors, it might be stated that a core group of genetic pathways are involved in the pathogenesis of IBD, which determine the interactions between these 3 aforementioned factors (fig. 2). Thus, in this model,

environmental factors are specifically affecting the content and function of the commensal microbiota, the intestinal epithelium and the immune system associated with the mucosal surfaces. Unfortunately, although a number of environmental factors have been identified by epidemiologic studies, the way in which they interact with the immune-genetic pathways as described in figure 3 are poorly understood, but interesting insights have emerged. For example, smoking, which protects from UC and promotes CD regulates T-cells, which in turn express the alpha 7 nicotinic acetylcholine receptors [17]. Chronic nicotine stimulation further promotes T-helper 1 (Th1) pathways, which are pro-inflammatory [18]. Furthermore, hemeoxygenase-derived carbon monoxide promotes bacterial clearance, suppresses macrophagic activity and enhances macrophage motility [19]. Appendectomy, on the other hand, which protects from UC prevents Th2-mediated colitis in animal models of IBD by preventing the development of T-cells with anti-bacterial specificity [20]. Finally, antibiotics that can both protect and promote IBD depending upon the time of life and the type of IBD that are associated with antibiotic exposure have major effects on the composition and function of the microbiota. Antibiotics can create profound effects in the microbial constitution of a host and result in durable and potential deleterious changes in the microbiota [21]. As such, it can be imagined that antibiotics cause the destruction of microbes that are potentially anti-inflammatory and beneficial such as *Faecalibacterium prausnitzii* [22]. Furthermore, broad spectrum antibiotics result in reductions of other Firmicutes and Lactobacilli and the persistence of Bacteroidetes and Proteobacteria in association with an increase in potentially inflammatory cytokines, which in their totality would be deleterious to the host [23]. Together, these observations support the notion that environmental factors are likely to impinge in precise ways on the specific elements that are critical to IBD pathogenesis; namely the commensal microbiota, intestinal epithelial cell and immune system.

Early Life as Critical Period in Which Genetic Environmental Influences Are Operative

One of the very important advances in the last several years is the genetic elucidation of the origins of the recent and increasing emergence of IBD during early life. Monogenic (single gene) defects have been recently demonstrated in association with IBD onset during the first 6 years of life suggesting highly penetrant genetic influences [2]. These genetic analyses have reiterated the importance of epithelial barrier function, neutrophil function, the regulation of inflammatory responses as well as adaptive immune activities in IBD pathogenesis. Interestingly, these studies and others have supported the important overlap between the pathways that are involved in VEOIBD and the complex IBD that develops later in life [5, 6, 24–27]. It is also interesting that the greatest increase in IBD incidence is found in children less than 9 years of age and especially in children from 0 to 4 years of age [28]. The increasing incidence in early life could represent increasing recognition in the medical community but it is just as likely that this represents a real increase in IBD during early life. These observations are also supported by animal models wherein influences in early life may be critical in the pathogenesis and onset of IBD, thus highlighting the critical influence between environmental and genetic factors in this critical period of development.

This brings us back to the concept of the hygiene hypothesis. This was first coined by Strachan [10] to explain the relationship between household size, birth order and hay fever in a birth cohort during 1 week in 1958 who were followed for 23 years. More recent data suggest that the hygiene hypothesis is really one that should potentially be renamed the microbial hypothesis as it imputes the importance of microbial factors and the pathogenesis of these complex disorders. These studies also suggest that early life influences on the immune system determine later life susceptibility to disorders such as IBD. Thus, disruptions of the microbiota or improper development of the immune system during early life are critical to the pathogenesis of these diseases. This makes it especially important to understand the environmental influences in early life and the relevant genetic elements. Interestingly, it has been shown that there is a strong association with antibiotics used in the first year of life and pediatric IBD [29]. Moreover, there is an inverse relation between asthma and IBD and has been shown amongst individuals who grow up on a farm [30]. Growing up on a farm appears to correlate to an exposure to a wider range of microbes than children in a more urban reference group, supporting the notion that critical microbial factors determine the development of the immune system and thus later-life IBD. In this regard, it is important to be reminded that the human microbiota acquired in early life by mother-to-child vertical transmissions and is subject to modification by a variety of environmental factors [31]. All mammals are born sterile although they may be influenced by microbial factors during gestation in the placenta. Upon birth, microbes are acquired from the environment, including the mother during movement through the birth canal. Thus, the variety of environmental factors may influence the mother's contribution of microbiota to her child, such as the exposure to antibiotics. Furthermore, neonatal and early life exposure of the infant may determine the combination of microbes to which the child is exposed. Microbial colonization of a child is a carefully choreographed process that involves early pioneer organisms followed by a variety of successor organism that determines the microbial community composition that reaches the adult like configuration by 3 years of age [32]. Early developmental events may be affected by diet as well as early-life antibiotics that have been associated with increased risk of IBD as noted [29, 31]. Parenthetically, it has been suggested that these microbial effects may be transmitted from generation to generation through this continuous process of neonatal interaction [33].

These early-life microbial influences are increasingly recognized to play a critical role in the development of the immune system associated with mucosal tissues such as the gut and the lung and potentially others [34]. It is clear that multiple different cell types are involved in the pathogenesis of IBD [3]. These cell types are likely to be under the influence of early life microbial factors. Important examples are the so-called natural killer T (NKT) cells that respond to (host) (self) or microbial lipids and determine immune responses at the mucosal interface [35]. NKT cells are very important because they interact directly with intestinal epithelial cells and are very important during the early phases of an immune response. Recent studies of NKT cells and CD1d that presents lipid antigens to NKT cells and activates them have revealed very important insights into the pathogenesis of IBD during early life and the critical influences that environmental influences have on this. It might be considered that there are 2 categories of environmental factors. The first are modifying factors, which are those that come before disease onset and do not cause disease in and of

themselves but ‘modify’, probably cumulatively and in critical periods of life, and in so doing determine host risk for disease. This suggests that these modifying factors may begin at the earliest days of life and cumulatively influence the development of IBD until a tipping point occurs. This tipping point might arguably be due to a second class of environmental factors which may be the so-called triggering factors. Triggering factors are the penultimate environmental event whose presence stimulates disease activity within a genetically susceptible host and initiates disease. Recent studies of invariant NKT (iNKT) cells have revealed that early life, but not later life, exposure to microbiota protects mice from high levels of iNKT infiltration into the colon and lung [36]. This has been shown in mice that are born germ free or whose mothers were treated with antibiotics and were then exposed to antibiotics in the first 2 weeks of life. Consequently, these germ free mice, which have very high levels of iNKT cells in the mucosal tissues of their colon, are highly susceptible to a chemically induced colitis caused by exposure to oxazolone. Re-colonization of the mice with microbiota or elimination of the antibiotics during the first 2 weeks of life, but not thereafter, normalizes the susceptibility to this environmental factor, oxazolone. Thus, immune programming (or education) by the microbiota in the first days of life is critical for determining later life susceptibility to disease induced by specific environmental factors that impinge on the specific immune pathway. It is further interesting, that these studies have revealed that one of the ways in which the microbial factors are regulating the immune system is by epigenetically modifying genes that regulate these pathways. Furthermore, it has been shown that specific microbial factors that are present in the early days of life are necessary for dampening the infiltration of the tissues with these potentially aggressive iNKT cells and preventing inappropriate susceptibility to environmental factors [37]. Thus in this paradigm, it might be stated that proper commensal exposure of the host is an important modifying factor and that exposure to certain environmental chemicals may be a triggering factor. It remains to be determined whether these observations in animal models have anything to do with human IBD; however, it is interesting that this pathway of iNKT cell expansion and activity has recently been shown to be operative and increased in young children less than 6 years of age with another iNKT cell dependent disorder; namely eosinophilic esophagitis (EoE) [38]. Comparing EoE during the first 6 years of life to children with EoE between 6 and 18 years of age or control subjects without EoE, there are increased concentrations of CD1d (the cell surface molecule that activates iNKT), transcripts for the T-cell receptor associated with iNKT, the chemokine ligand associated with promoting iNKT infiltration (CXCL16) and inflammatory factors associated with this disease (LTC₄S). Interestingly, only those children with EoE that were responsive to dietary restriction of foods that promote EoE exhibited a diminution in this pathway based upon gene expression of afflicted tissues. Moreover, the children with activation of this pathway were more likely to be exposed to antibiotic based on retrospective surveys.

What Is the Future?

In light of the increasing recognition that environmental factors are critical to the pathogenesis of IBD through their effects on particular immuno-genetic pathways, it is essential that the community both better understands the way in which we currently define epidemiologic factors for IBD risk as well as understand and potentially define others that

may be involved. In the latter case, this will require much better tools for defining the so-called envirome or exposome [39]. In addition, it is hoped that through enabling increasing power to perform multi-omic analysis of IBD that integrates knowledge derived from the host genome or transcriptome, the microbiome or metatranscriptome and other potential omic databases including the metabolome, proteome and immunome together with metaclinical data, we will be better able to understand these disorders and develop enhanced predictive tools.

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Fig. 1.
A model for the syndromic nature of IBD. Adapted from Kaser et al. [¹].

Fig. 2. Model for the interaction between genetics and environment in IBD. Adapted from Kaser et al. [3].

- Unfolded protein response and autophagy pathways (e.g. *XPB1*, *ATG16L1*): *ability to tolerate the performance of innate and/or adaptive immune responsibilities*
- Epithelial barrier function (e.g. *ITLN1*, *MUC19*): *the ability of the epithelium to regulate microbiota and their translocation*
- Innate immunity (e.g. *NOD2*, *CARD9*): *inappropriate bacterial sensing and clearance by innate immune cells*
- Adaptive immunity (e.g., *IL-23R*, *STAT3*, *JAK2*, *TYK2*, *IL-10*): *imbalance between effector (inflammatory) and regulatory (anti-inflammatory) pathways*
- Inflammation pathways (e.g. *MST1*, *CCR6*, *IL6ST*): *dysfunction in leukocyte recruitment and inflammatory mediator production and response*

Fig. 3.

A parsed view of the immuno-genetic pathways that interact with environmental influences. According to Kaser et al. [³].