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Microbiome-Epigenome Interactions and the Environmental Origins of Inflammatory Bowel Diseases

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Abstract

The incidence of pediatric Inflammatory Bowel Disease, which includes Crohn's and ulcerative colitis, has risen alarmingly in the Western and developing world in recent decades. Epidemiological (including monozygotic twin and migrant) studies highlight the substantial role of environment and nutrition in IBD etiology. Here we review the literature supporting the developmental and environmental origins hypothesis of IBD. We also provide a detailed exploration of how the human microbiome and epigenome (primarily through DNA methylation) may be important elements in the developmental origins of IBD in both children and adults.

Introduction

Inflammatory Bowel Diseases (IBD), including Ulcerative Colitis (UC) and Crohn's Disease (CD), are disorders characterized by chronic inflammatory destruction of the gastrointestinal mucosa(1). The etiology of IBD is unknown, but the diseases are thought to arise secondary to an uncontrolled mucosal immune response in the background of host genetic susceptibility, environmentally induced predisposition, and gut microbial dysbiosis. The key feature of pathogenesis is believed to be a dysregulated immune response against the commensal microbiota(2).

A recent systematic review chronicles the relative contribution of genetics, nutrition, environment, and other factors on early-onset vs. late-onset IBD(3). For children with rare, very early-onset IBD, genetic predisposition appears to play a more important role, while environmental factors and gut microbiota are likely more involved in the disease etiology

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and natural history of patients who present with the diseases at a later age. The incidence of IBD, particularly in pediatric populations, has been rising in the Western world and in developing nations at an alarming rate(4–6). The prevailing theory behind this surge in light of the geographical distribution of IBD is that the environmental and nutritional factors associated with Westernization are at fault(7). The purpose of this review is to highlight the environmental and nutritional origins hypothesis of IBD. We will further explore how select environmental and nutritional factors may affect host epigenetics and commensal microbiota.

Epidemiological Evidence Supports The Environmental Origins of IBD

General Epidemiology of IBD

IBD prevalence is highest in Western Europe, North America, and Australia and steeply declines outside of the developed world(8,9). In recent decades, however, IBD incidence has increased in previously low prevalence areas, such as South America and Asia, and is thought to be correlated with industrialization and Westernization(8,10). Particularly, pediatric IBD incidence is increasing at an alarming rate in both developed and developing countries,(8,11) although some investigations indicate a relative stabilization of incidence in certain high prevalence areas(12). Generally, UC appears before CD where IBD is on the rise(11). Many of these observations may be a byproduct of increased physician access and improving healthcare systems in developing nations. The rise in IBD, however, that has been observed in Eastern Europe, a region of comparatively quality healthcare, over the last 25 years strongly associates with the steady appropriation of a Western lifestyle(13–15). Prevalence of IBD follows a North-South gradient in the United States and an East-West gradient in Canada. These gradients likely reflect differences in population density, urbanity, and environmental exposure within each nation rather than genetic differences or access to healthcare(16–18). A recent meta-analysis of previous epidemiological studies, mostly from North America and Western Europe, discovered a modest, though significant, increase of pediatric CD incidence associated with increasing latitude and low daily ultraviolet radiation levels (19). The authors suggest that diminished daily ultraviolet radiation levels at higher latitudes might affect vitamin D synthesis, immunologically predisposing children to the disease. Within-region observations, such as the above, dampen the theorized role of genetics and point to the greater contribution of environment and nutrition in IBD etiology.

The Environmental/Nutritional Origins of IBD

The rise in IBD incidence in developed and developing nations has coincided with a plethora of factors associated with Westernization including improved hygiene, increased access to and consumption of food that has changed in composition and processing, sedentary lifestyle, antibiotic use, refrigeration, urbanization, etc. (described, briefly, in Table 1). It should be emphasized that many of the environmental/nutritional factors contributing to IBD have been disputed or questioned in the literature. Furthermore, there are several considerations that are important to exercise when assessing environmental factor contribution to IBD etiology:

1. IBD is specific to humans (since similar disorders are still markedly different even in non-human primates(20)). Therefore, animal environmental/nutritional model studies of IBD etiology are inherently flawed.
2. Dependable results from human epidemiologic studies (even if prospective and well-controlled) are very difficult to attain for ethical and technical reasons(21).
3. Secondary to the limitations above, it is almost impossible to exclusively examine a single environmental factor in human IBD etiology.

In regard to the third consideration, we bring a few examples to demonstrate the complexity and interactive nature of environmental elements relevant for IBD pathogenesis based on epidemiologic and animal model studies.

First, increased n-6 polyunsaturated fat (PUFA) consumption has been associated with UC development in a large scale human prospective trial(22). Concomitantly, one major dietary source of n-6 PUFA is fried foods, which have been observed as significant component of a pre-illness diet in Crohn's disease patients(23). Additionally, consumption of potato skin derived glycoalkaloids (through French fries, for example) has been shown to worsen colitis in 2 different mouse models of IBD(24). These studies underscore the complex dietary attributes of one single nutritional component (n-6 PUFA linked to fried foods in this example) that can be relevant for IBD development. In a recent work, we have not found any significant effect of isolated n-6 PUFA supplementation on acute colitis susceptibility in mice. Rather, the transient pediatric supplementation of n-6 PUFA resulted in acute colitis protection in young adult animals(25).

For our second example illustrating the difficulty of associating any single environmental factor to IBD etiology, we examine the proposed contribution of refrigeration, as a consequence of industrialization, to the development of CD(26). It is thought to do so by inducing increased exposure to psychotropic bacteria such as *Yersinia spp* and *Listeria spp* (i.e. the cold-chain hypothesis). This hypothesis was further substantiated by a record of significantly earlier pediatric exposure to a home fridge in CD patients than in controls(27). The consumption of refrigerated foods, however, has many secondary effects that could be relevant for IBD pathogenesis. Refrigeration results in the consumption of less pickled food and increases dietary diversity, both of which are highlighted as major characteristics of the Westernization of global dietary habits.(28). The consumption of acetate (a major component of pickling), for instance, has been shown to be protective against murine colitis(29). Additionally, we have highlighted the potential for increased dietary diversity to possibly contribute to IBD pathogenesis based on a murine colitis model and human epidemiology(30). Consequently, decreased consumption of pickled foods and increased dietary diversity resulting from the expansion of refrigeration may be important contributors to its association with IBD development (in addition to the hypothesized cold-chain effect). Importantly, both acetate and dietary diversity have functional and compositional relevance to the intestinal microbiota, emphasizing its physiologic role in communicating environmental/nutritional exposures to host physiology and pathology.

In spite of the difficulties in interpreting environmental influences on IBD susceptibility, an emerging common theme from animal model(31,32) and human epidemiological observations is that pediatric (especially infantile) disruption of the gut microbiome maturation process can significantly contribute to colitis susceptibility in animals and to IBD in humans. Prematurity, infantile exposure to antibiotics, pediatric exposure to refrigeration (see above), and plausibly all environmental factors relevant in IBD etiology can have significant effects on gut microbiota composition during critical periods of development. Microbiome composition changes during such developmental periods may lead to persistent modifications in host physiology (and vice-versa) that could alter predisposition to IBD later in life. This will be discussed further in a later section.

Migrant Population Studies

Interestingly, studies focusing on immigrants further point to a substantial contribution of environment and diet to IBD incidence. Migrants represent a unique study cohort – clearly, the genetic susceptibility of an immigrant to IBD remains static, yet they experience a dramatic change in environment and diet upon arrival to a new country. Epidemiological evidence suggests that exposure to environmental factors associated with IBD has greater influence on IBD incidence during early life, although transient exposures to higher levels of industrialization even in young adulthood may increase one's chances for developing UC(33). Recent studies, conducted in Canada and Sweden, show that immigrants have lower IBD incidence, with decreasing risk for each additional year of age at immigration(6,34). Furthermore, children of some, but not all, migrant groups are less likely to be diagnosed with IBD(6). The heterogeneity of IBD incidence appropriation in children of migrants indicates that early life exposure to a Western environment cannot exclusively predict likelihood of disease. Variation in different ethnic groups towards preserving dietary habits within the family following migration, however, could explain the heterogeneous IBD incidence in first generation immigrant children. This latter hypothesis would imply that nutritional influences are more important in IBD pathogenesis during postnatal pediatric development than other environmental factors. Second generation immigrants, however, have a similar IBD incidence rate as non-immigrants(35). These studies indicate that environmental exposures (including maternal diet) in prenatal life and during pediatric development (perhaps diet being the most important postnatally) are more critical than genetic predisposition towards IBD pathogenesis.

Genetics and Monozygotic Twin Studies

Over 160 genetic susceptibility loci have been linked to IBD(36). The vast majority of these loci contribute to disease development with low odds ratios (1-1.5) revealing the complexity of the limited genetic attribution (13.6% for CD and 7.5% for UC) to these disorders. There is also diverse genetic susceptibility to IBD in different ethnic backgrounds in spite of similar disease phenotypes(37–41). This genetic diversity suggests that changes common to industrialization induce non-genetic modifications in genetically vulnerable hosts that may be more important than the genetic predisposition itself towards inducing disease.

Observations in monozygotic (MZ) twins revealed low concordance for IBD within pairs. Concordance rates are overall less than 50% for IBD with CD higher (27-56%) than UC

(15-19%)(42). This suggests that genetic predisposition is insufficient for IBD development – and that environmental factors are playing a bigger role in disease pathogenesis, especially in UC. In the meantime, it is MZ twins who, unless they are raised apart, share the same environmental and nutritional influences. Therefore, based on MZ twins, genetic and epidemiologic observations, it appears that genetic predisposition and shared environment/ nutrition only heighten the probability of developing IBD, but are insufficient to instigate the onset of disease. Stochastic biological factors influenced by genetics and the environment appear to be key elements in the pathogenesis of the disorders (Figure 1.). Although frequently overlooked, physiologic noise (or stochasticity), defined as an unpredictable disturbance to a biological system, is an inherent part of human biology(43,44). IBD are prime examples where physiologic stochasticity is likely to play a significant etiologic role(45). It is, of course, mindboggling to consider that unique instigators may offset each case of IBD stochastically within the complex and interactive biologic systems involved in the pathology of the diseases.

Criteria for Interactive Systems

Out of these interactive systems, the microbiome and the host epigenome fulfill certain criteria, which make them prime candidates for communicating the environmental, nutritional, and developmental origins of IBD. Such criteria are:

1. Developmental maturation/modification - Biologic systems that are in flux during critical developmental periods are most likely to respond to environmental stimuli
2. Environmental/nutritional responsiveness
3. Stability once adjusted to environmental/nutritional influences
4. Penetrance (i.e. able to convey phenotypically relevant effects)

In the next section, we will highlight how the epigenome and the commensal microbiome fulfill the above criteria.

The Microbiome and The Host Epigenome are Potential Elements in The Environmental Origins of IBD

The Microbiome in the Environmental Origins of IBD

The human microbiome is defined as the complete population of bacteria, fungi, and viruses that live in and on the human body (all their molecular components as well, dead or alive) (46). In humans, the gastrointestinal system houses the largest quantity and diversity of microbiota (i.e. the live microbiome)(47). Generally, the enteric microbiota exists in symbiosis with the host, and plays important roles in digestion, immune system maturation, and epithelial barrier integrity, in addition to acting as a competitive “barrier” to pathogenic invasion(48). The microbiota can act as an environmental sentinel, able to quickly respond to external stimuli such as dietary/environmental change, with protein-coding bacterial genes outnumbering human host genes approximately 360:1(49).

Gastrointestinal microbiome composition, microbial function, and metabolic activity of gut microbiota are perturbed in patients suffering from IBD, though whether this is an initiator

or consequence of the disease is unclear(50,51). Abnormal secretion of antibodies against common commensal microbiota, including common enteric fungi, in IBD-affected tissues suggests that the mechanisms responsible for tolerance induction are obstructed(52,53). A dysregulated immune response toward enteric microbes results in the down-regulation of tight junction proteins, allowing bacteria to infiltrate the epithelial barrier(52,54–56). This results in further inflammation and exaggerates dysbiosis (i.e. abnormal microbiome composition)(54,57). The current paradigm states that IBD pathology is characterized by an aberrant inflammatory response to microbiome, resulting in the subsequent destruction of the gastrointestinal mucosa and further bacterial/microbial encroachment.

In relation to the nutritional and environmental origins of IBD, the microbiome appears to be an important element in postnatal life by fulfilling the above outlined “systems criteria”:

1. The human microbiome goes through an intense evolution from birth that stabilizes following 3 years of age, but proceeds at lower velocity to young adulthood(58,59). Therefore, environmental influences such as infantile exposure to antibiotics, pediatric exposure to refrigerated foods, and even young adulthood exposure to high levels of industrialization could modulate its composition to promote IBD.
2. The human microbiome is highly responsive to nutritional changes. Rapid microbiome shifts can occur upon drastic dietary modification even in adults,(60) where microbiome composition is otherwise relatively stable over several months to years(61). The microbial dietary shifts appear to depend mostly on the nutritional impact, rather than the host genotype based on murine studies(62). Therefore, it is conceivable that environmental/nutritional changes of industrialization could induce similar IBD prone microbiome modifications in different ethnic backgrounds.
3. As previously stated, the human microbiome possesses stability(61). Individual microbiomes remain separated in spite of significant nutritional changes over short periods of time in adults, and long-term dietary influences link to distinct enterotypes(63). Therefore, once a nutritional change modifies the microbiome during a critical developmental period (i.e. childhood), IBD promoting characteristics could be carried on to young adulthood, when the onset of disease peaks. We have observed both transient(64) and persistent(25) microbiome-associated pediatric dietary influences to modulate IBD predisposition in young adult mouse models.
4. The mammalian, including human, microbiome can modulate the host phenotype. A large number of emerging studies utilizing broad-spectrum antibiotics and fecal microbiota transplantation into germ free animals(65) or even humans with disease(66) show the significant phenotype-modulating capacity of the microbiome. Our work demonstrates that mice fed a high n-6 fat diet in early life show prolonged protection against DSS-induced colitis, but only when the diet is reversed prior to insult. Critically, this protection appeared to be mediated by the microbiota as transplantation of the n-6 microbiome into germ free mice transmitted significant protection against colitis(25). Similar studies demonstrate that capacity of the microbiome to transmit the metabolic phenotypes of the

donor(67,68). The most clinically relevant application of the transmissive properties of the microbiome is in the treatment of *C. difficile* infection. Fecal microbiome transplantation not only restores microbiome composition/function, it also reinstates normal bile acid composition and re-establishes gut homeostasis(69–71).

The Epigenome in the Environmental Origins of IBD

Epigenetic changes define molecular modifications that alter gene expression independently from genetic alterations in the DNA. Such functionally relevant genome-wide molecular modifications are frequently referred to as the “epigenome”. The epigenome may also be an important etiologic element in the environmental origins of IBD by fulfilling the above outlined “systems criteria”:

1. Epigenetic programming occurs during the prenatal and post-natal stages of life. A large, longitudinal (from birth to 18 months of age) study in twins has demonstrated that the epigenome changes rapidly in early life(72). Increasing epigenetic discordance between twins over time further underscores the role of non-shared environmental factors and, in part, stochasticity in the development of the epigenome during early life(72). Mouse studies highlight the post-infantile epigenetic maturation of the colonic mucosa as well(73). These findings indicate that the epigenetically responsive/vulnerable period in respect to colitis predisposition extends beyond infancy in mammals.

2. The human epigenome is responsive to environmental and nutritional changes(74). In mammals, supplementing the murine maternal diet with methyl-donor micronutrients can induce pronounced changes in colonic mucosal gene methylation and this associates with augmented colitis predisposition in the offspring(73,75,76). In Wistar rat offspring, a gestational diet rich in multivitamins inflicted specific epigenetic alterations, particularly affecting metabolic pathways(77). However, epigenome responsiveness is likely not limited to the prenatal period as our murine studies suggest that epigenetic maturation in the colonic mucosa continues post-natally through pediatric development (73). Similar findings in neonatal pigs have been made(78). In a study of preadolescent humans, quality of dietary fat consumed influenced DNA methylation of genes specifically involved in metabolic syndrome(79) underscoring the nutritional responsiveness of the human epigenome during childhood.

3. Epigenetic modifications, particularly DNA methylation, are stable over time. As mentioned above, supplementing the murine maternal diet with methyl-donors induced methylation changes still identifiable 3 months into the post-natal period(80). Perhaps the most famous example regarding environmental responsiveness of the epigenome in humans is the infamous Dutch Hunger Winter, throughout which pregnant women were deprived of food and nutrients during wartime – the effects of this prenatal programming were discernable in their children nearly 6 decades later (81).

4. Epigenetic changes in response to stimuli may exert phenotypically relevant effects in health and disease. The concept of epigenetic disease origins is erupting in all areas of medicine from neurology(82) to cardiology(83) and anesthesiology.(84) The potential importance for epigenetics in IBD was raised in 2000,(85) but is only recently receiving more attention(2,7,86,87). Although other epigenetic mechanisms besides DNA methylation may contribute to the development, progression and/or maintenance of IBD (e.g., histone modifications(86,88,89) and microRNAs(90–93)), only DNA methylation has been shown to be stably transmitted through repetitive cell divisions,(94,95) thereby having the capacity to permanently convey epigenetic information during the lifetime of an individual. Additionally, only DNA methylation has been described to directly communicate environmental exposures to phenotypic outcome in mammals(96). Recent work from Scotland has identified differentially methylated regions (DMRs) in peripheral blood leukocyte (PBL) DNA derived from treatment naïve pediatric CD patients(97). However, these had significant co-localization with IBD susceptibility single nucleotide polymorphisms (SNPs) indicating their genetic origins. As opposed to the Scottish study, we, in untreated pediatric IBD patients from the US, could not identify significant PBL DMRs following SNP exclusion despite using similar methodology(98). Significant cell-subset, variation-induced epigenetic noise in PBL may also interfere with consistent findings(99). Colonic mucosa, as the end-organ of IBD, has naturally been a tissue where DNA methylation associations of the disease group were extensively studied. Targeted(100) and non-biased(101) assessments of DNA methylation detected numerous colonic mucosal associates of inflammation in IBD. IBD treatments can modulate DNA methylation,(102) and most previous GI mucosal studies examined patients following treatments. We recently studied treatment naïve pediatric IBD cases and discovered a remarkable colonic mucosal epigenetic separation of UC compared to CD(103). Functional methylome studies indicate that such modifications may impact gene transcription relevant to UC(104). Our findings however, implicated that the majority of UC-specific DNA methylation variation resulted from mucosal inflammation and did not persist in patients achieving treatment-induced remission.(103) Therefore, much work needs to be done in the future to overcome the difficulties of epigenetic etiology research in humans. Causation-centered mouse studies, however, suggest that the epigenome's response to a nutritional stimulus can modulate colitis predisposition in mammals(80).

Epigenome-Microbiome Interactions

We have already indicated that the host epigenome and the commensal microbiota are likely to act in concert to modulate IBD predisposition secondary to environmental/nutritional exposure during critical periods of life. This potential has been highlighted by others as well in recent reviews(105,106). Briefly, pathogenic and commensal microbiota (and their metabolites) may contribute to epigenetic changes in their human hosts through a variety of mechanisms. Pathogenic bacteria may initiate host epigenetic modifications to inhibit immune response to invasion and to encourage proliferation of infected tissues(107,108). Interestingly, a recent investigation by Chernov, *et al*. demonstrated that *Mycoplasma*, a

common intracellular pathogen in colonic epithelia, produces DNA methyltransferases (DNMTs: enzymes catalyzing DNA methylation). As illustrated in Figure 2B, the mycoplasmal DNMTs had the capacity to localize into the host nucleus and alter host DNA methylation at genomic regions not methylated by host-derived DNMTs (109). These findings suggest that microbes could directly induce long-lasting unique epigenetic changes in the host.

Commensal microbiota may also epigenetically modify the host genome through the production of Short Chain Fatty Acids (SCFAs) such as butyrate, through generating biotin and folate, and though their interaction with Pattern Recognition Receptors (PRRs) on cell surfaces (summarized in Figure 2C).

Butyrate is produced by bacteria as a consequence of dietary fiber digestion and is important for intestinal health(107,110). Well-studied groups of butyrate-producing bacteria include *Faecalibacterium prausnitzii* and many of the *Roseburia* species(111). The reduced representation, and sometimes complete absence, of these butyrate-producing bacteria is repeatedly observed in the gastrointestinal microbiome of both UC and CD patients(112–116). A number of *in vivo* and *in vitro* studies suggest that butyrate acts as a major nutrient for colonocytes, and can dampen intestinal inflammation (in part) by suppressing nuclear factor-B (Nf-kB) activation. Butyrate can also promote epigenetic remodeling in intestinal stem cells by acting as a histone deacetylase inhibitor(117–120). In UC patients, butyrate uptake is reduced in colonocytes and elements of the butyrate oxidation pathway are impaired(121–124). Concordantly, a double-blind, placebo-controlled clinical trial in UC patients demonstrated that supplementation of rectal 5-ASA enemas with butyrate resulted in a significant amelioration of disease activity(125). Biotinylation, the epigenetic process in which biotin is attached to histone groups, is important for suppressing retrotransposon activity and maintaining chromosomal stability. The human body uses diet- and bacteria-derived biotin to achieve this, as it is incapable of synthesizing its own (110). Some commensal genera (namely, *Lactobacillus* and *Bifidobacteria*) affect the bioavailability of methyl groups through their production of folate(126). Folate feeds into the one-carbon metabolism cycle, regulating methyl-donor availability and eventually can affect DNA methylation. *Bifidobacteria* and *Lactobacillus* populations are reported to be significantly reduced in IBD patients, and are associated with disease severity, though the mechanism of action is still unclear(127–129). Reports of blood folate concentrations in IBD patients are inconsistent: some groups report folate deficiency, while others present evidence for significantly higher folate concentrations in affected individuals(130–133). A potential, unexplored explanation for these inconsistent reports is that variability in microbiome composition between patients may be linked to folate bioavailability and resulting systemic concentrations of the molecule.

Microbiota interact with intracellular and extracellular PRRs, resulting in transcriptional responses critical to tissue development, immunological maturation/surveillance, and normal physiological function (summarized in Figure 2D). Toll-like receptors (TLRs) are critical microbiome surveillance receptors as they bind microbe-associated molecular pattern (MAMP) molecules. These molecular interactions can stimulate the emergence of appropriate crypt-villus architecture in the intestinal mucosa. Germ free mice have an

overall abnormal architecture of the gastrointestinal epithelium which can be rescued by microbial colonization(134,135). Immunologically, microbiota-mediated signaling through PRRs is essential for the post-natal maturation of gut-associated lymphoid tissue (GALT) (136), direct the conversion of CD4(+) T cells into Foxp3(+) T-regulatory cells(31,137), and are required for the establishment of a proper T_H1/T_H2 balance after birth(138,139). Furthermore, colonic region-specific TLR2 and TLR4 expression has been reported in SPF, but not germ-free mice, and microbiome transplantation reverses this region-specific expression pattern(140). It was later discovered that this microbiota-induced, region-specific expression associated with epigenetic alterations in the involved genes(141,142). In this way, commensal microbiota may modulate TLR expression, priming the host to respond to pathogenic threats later on. Later in life, microbe-mediated signaling via PRRs primarily affects gut homeostasis. Signaling through the TLR receptors, for example, regulates tight-junctions to maintain epithelial barrier integrity and stimulates the secretion of anti-microbial peptides to control commensal microbiota composition(143). Importantly, commensal microbiota are lifelong immunomodulators, promoting the intestinal expression of cytoprotective genes while suppressing pro-inflammatory genes(143).

The conceptualization of the microbiome as an epigenetic modulator is steadily gaining attention as researchers have begun to associate overall commensal microbiome composition, rather than select species, with epigenetic profiles in mice and in humans(141,142,144). Successive work has recently indicated strong associations between gut microbiome composition and promoter methylation of genes relevant for lipid metabolism, obesity and inflammation in PBL DNA(144).

Conclusion

Though a great many environmental and nutritional factors have been implicated in IBD, none have proven to be causal. This review presents a unique intersection of several compelling lines of evidence suggesting that environment and diet, through their profound effects on gut microbiome function and host epigenome modification, may play a primary role in IBD pathogenesis. This realization will hopefully fuel the near-future development of novel nutritionally- and epigenetically-focused preventative and therapeutic interventions for this highly morbid disease group.

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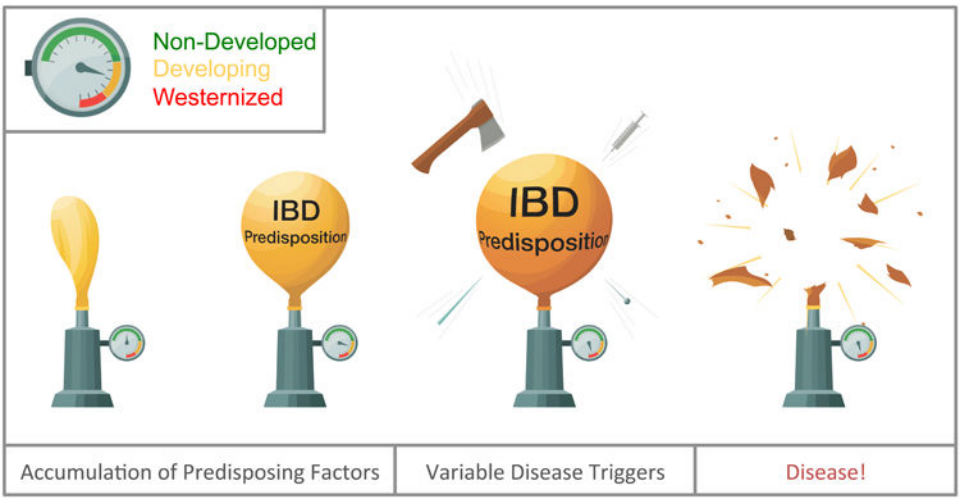

Figure 1.

Schematic demonstration of the role of stochastic biological factors in the initiation of IBD. In genetically predisposed individuals, environmental and nutritional factors contribute to IBD predisposition (balloon inflation), where degree of predisposition positively correlates with Westernization/urbanization (pressure gauge). Stochastic biological factors (sharp objects), however, give impetus for the onset of the disease. Such factors may exert their critical effect in any of the intercalating biological systems that participate in IBD pathogenesis. Disease presentation is similar, however, irrespective of the critical trigger secondary to the intimately interactive systems (microbiome-mucosa-immune system).

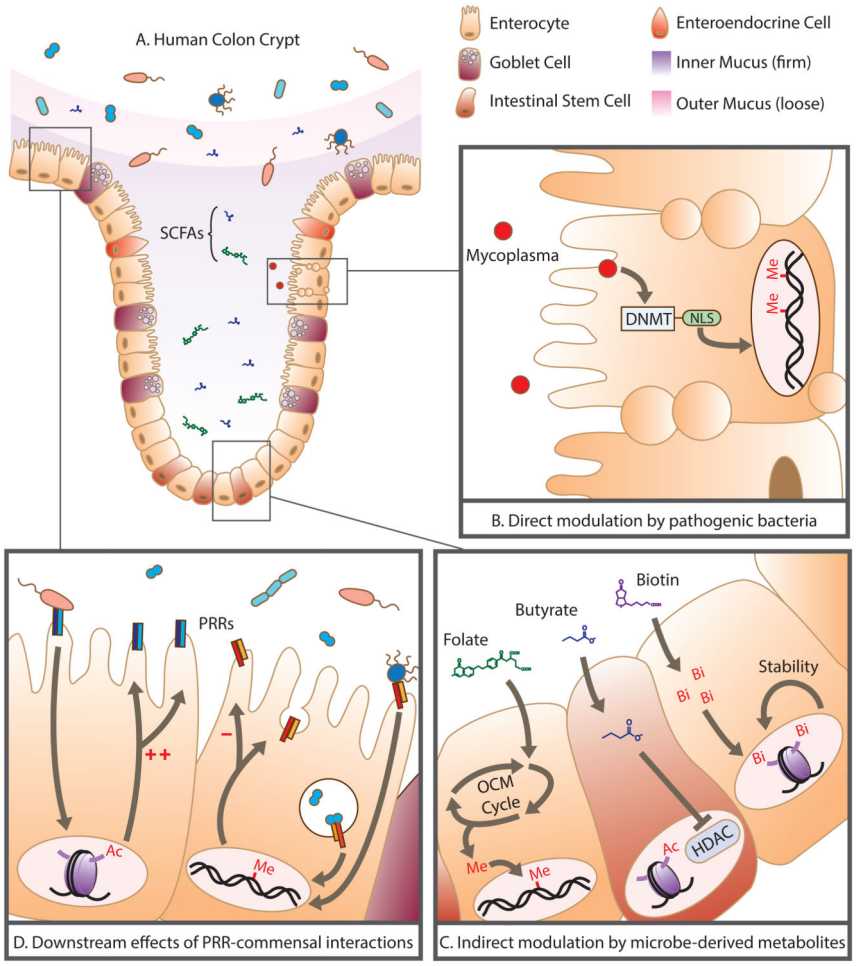

Figure 2.

Direct and indirect modulation of the human epigenome by pathogenic and commensal microbiota: (A) Human colonic physiology and its spatial relationship with the microbiome and the short chain fatty acids (SCFAs) and metabolites it produces. (B) Mycoplasma, an intracellular microbial pathogen, synthesizes DNA methyltransferases (DNMT) complete with nuclear localization signals (NLS) that penetrate the host nucleus and result in *de novo* methylation. (C) Microbe-derived metabolites (folate, butyrate, and biotin) indirectly modulate the host epigenome: Folate enters the one carbon metabolism cycle (OCM Cycle) to affect the bioavailability of methyl groups, butyrate acts as a potent histone deacetylase (HDAC) inhibitor, biotin availability for biotinylation promotes chromosomal stability. (D) Commensal interactions with pattern recognition receptors (PRRs) cause downstream transcriptional changes, mediated primarily through methylation and acetylation, resulting in increased/decreased production of PRRs as well as extra-epithelial responses.

Table 1

Non-exhaustive description of environmental/nutritional factors identified in epidemiological studies as being associated with IBD and the known effects of those factors on the microbiome and epigenome. Importantly, many of these factors have been disputed or questioned in the literature, repeatedly emphasizing the limitations of human epidemiologic observations.

	Factor	Observed IBD Associations	Effects of Factor on Microbiome	Effects of Factor on Epigenome
Encironmental	Helminth Infection	Protective against IBD [145,146]	Reduces bacterial attachment, alters community structure, increases diversity [147,148]	Affects methylation signature in host T-cell response [149]
	Antibiotic Use in Childhood	Strongly associated with CD incidence but generally not withUC[150-153] Antibiotic use for treatment of gastroenteritis – strongly associated with both UC and CD [150,154,155]	Antibiotic use has substantial effects on microbiome composition/ function, decreases diversity over time, and predisposes hosts to infection [156]	Antibiotics have trans-generational effects on sperm viability in insect models [157]
	Urbanization	IBD incidence is high in urban environments [158-160] Rural, farming upbringing is protective against IBD[161] Air pollutants may increase risk of early onset IBD [162,163]	Rural and urban community structures and functions differ [164,165]	Insufficient Information
	Smoking	Protective (and therapeutic) in UC [166-168] Associated with increased risk and prognosis in CD [169-171]	Cessation in results in increased microbial diversity; gut microbiome composition changes to one associated with improved energy harvest [172,173] CD patients that smoke have clinically relevant dysbiosis [174]	Maternal smoking – persistent, altered methylation of development- and metabolism-associated fetal genes [175-179] In adults – global, persistent methylation changes [180-182]
	Preterm Birth	Increases risk of IBD [183]	Reduced diversity, high risk of pathogenic colonization, decreased stability [184]	Extreme preterm birth transiently affects methylation profile; select regions show persistence into adulthood[185]
	Gastroenteritis	Strongly associated with increased IBD risk [150,154]	Intestinal microbiota can promote infection with and replication of enteric viruses [186,187]	Insufficient Information
	Mycobacterial Infection	*M. avium paratuberculosis* (MAP) frequently identified in CD patients [188-190]	Insufficient Information	*MAP* inhibits chromatin remodeling in host macrophages [191]
	Appendectomy	Protective for U C [192-194] More frequent, though not a risk factor, for CD [193-196]	Limited evidence suggests microbiota in normal and diseased appendixes differ [197]	Insufficient Information
Nutritional	Breastfeeding	Generally found to protect against IBD [198]	Promotes microbial homeostasis and microbiome plasticity later in life [158,199,200]	Breast milk contains SCFAs, which have epigenome-modifying properties (including DNA methylation and histone modification)
	Non-Western Dietary Practices	Fasting protected against (murine) colitis; lack of fasting	Variable diet reduces microbial diversity in mice [30]	Caloric restriction during the prenatal and adolescent periods has

	Factor	Observed IBD Associations	Effects of Factor on Microbiome	Effects of Factor on Epigenome
		predisposes colitis, presumably leptin-mediated [201-205] Monotonous diet protects against colitis in humans and murine models [30,206]	Fasting alters microbiome composition and diversity in species – dependent manner, generally associated with reduced inflammation [207-209]	potent, persistent effects on DNA methylation [81,210-212]
	High Fat / High Carb Diet	High intake of trans-unsaturated fat associated with increased UC risk; High intake of long-chain n-3 fatty acid associated with reduced UC risk[213] However, dietary reversal after n-6 fat consumption protects against murine colitis [25]	Stimulate expansion of organisms within the microbiome that are efficient at energy harvest which then promote inflammation, hyperphagia, hyperlipidemia, gut permeability, etc. [68,214]	Associated with specific methylation differences affecting metabolic pathways in pediatric population [79]
	Dietary Fiber	Increased fiber consumption [215] Cellulose supplementation ameliorates murine colitis [64]	Decreased fiber consumption dramatically alters composition, gene content, richness, and SCFA production [206]	Dietary fiber is fermented to release SCFAs, which have validated epigenome-modifying properties (including DNA methylation and histone modification) [216,217]
	Dietary Protein (meat and dairy)	Diet high in animal protein increases risk of IBD [218]	Reliably alter composition and function: Increase in bile-tolerant organisms, fewer (anti-inflammatory) butyrate producers[60]	Insufficient Information
	Vitamin D	Latitude associates with IBD risk, presumably due to Vitamin D intake [17,19]	Regulates gut microbiota to protect against colitis in mice [219] Vitamin D deficiency increases *C. difficile* infection risk [220,221]	Pre-natal vitamin D deficiency epigenetically reduces immune cell development in mice [222]
	Food Additives	Dietary emulsifiers promote murine colitis and metabolic syndrome in a microbiome mediated manner[67] Micronutrient supplementation of maternal diet augments murine colitis in microbiome-mediated manner[75,76]	Emulsifiers alter microbiome composition and function, microbiome transplant of treated mice results in metabolic disease in recipient [67] Artificial sweeteners induce microbiome-mediated glucose intolerance[65] Maternal methyl donor supplementation alters murine clonic mucosal microbiome, arguments colitis [76]	Supplementation of murine maternal diet with methyl donors modified colonic mucosal epigenome and conferred colitis susceptibility[80]
	Refrigeration	Associates with CD development[27]	Insufficient Information	Insufficient Information