Unraveling the Multifactorial Pathogenesis of Inflammatory Bowel Disease: Systems Biology Insights into Host Genetics, Environmental Exposures, and Gut Dysbiosis

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ABSTRACT:

Inflammatory Bowel Disease (IBD) is an umbrella term for two separate chronic conditions, Crohn's disease (CD) and ulcerative colitis (UC), which are now a major health problem in the world. This change is similar to the process of urbanization and westernization that is taking place all over the world. In this review, we explore the multifaceted “perfect storm” of factors that influence IBD, all of which interact to cause disease, including genetic predisposition, environmental triggers and an imbalance of gut microbes. Identical twins don't always get the disease, and although genetics are a clear factor, particularly in Crohn's, this means they are not a direct cause. Rather, the current "exposome" seems to require "insults" to the environment as its catalysts. We focus in particular on the dangers of the western diet, including its lack of fiber, which is crucial for delivering important short-chain fatty acids to the gut, and the role that common food additives may have in damaging the gut lining. The review also discusses the "IBD paradox" on smoking and the "hygiene hypothesis" which states that a too sterile early-life environment could lead to an under-trained immune system. The root of this imbalance is the gut microbiome. A reduction in the diversity of microorganisms, the loss of protective bacteria such as *Faecalibacterium prausnitzii*, and the presence of "pathobionts", such as Adherent-Invasive *E. coli*, are features of IBD that are always observed. These changes cause a weakened intestinal barrier and inability of the body's innate immune system to remove threats, creating a constant, self-perpetuating immune response against the gut. We explore these interactions in the context of epigenetics and demonstrate how the DNA of our bodies is physically ‘marked’ by our environment. In conclusion, we suggest that the next generation of patients with IBD should be treated in a precision medicine fashion and thus restore a unique ecological and immune balance in each patient.

KEYWORDS: Crohn's disease, Pathobionts, Gut microbiome, Gut, Immunity, Inflammatory Bowel Disease (IBD)

1. Introduction

Inflammatory Bowel Disease (IBD) has become a public health problem of the world and no longer a medical curiosity of the west. Crohn's disease (CD) and Ulcerative colitis (UC) are the two main phenotypes of inflammatory bowel disease (IBD) characterised by similar clinical features as chronic diarrhoea, abdominal pain and systemic inflammation, but have a fundamentally different pathogenesis. Transmural inflammation of any segment of the gastrointestinal tract with strictures and fistulas are features of CD. In contrast, UC is confined to the colonic mucosa and does not involve the rectum and is found in a continuous fashion. [1,2,3] In recent years, biomedical engineering and systems biology have led to a dramatic increase in the number and variety of tools that can be used to study complex diseases like

inflammatory bowel disease. New technologies such as high throughput sequencing, multi-omics systems, and computational modelling enable integrated analysis of host genetic, environmental exposure, immune response and gut microbiome dynamics. These technologies will help researchers investigate the nature of IBD as a system-level disease instead of a series of individually isolated events. The first hint at the etiology of IBD is given by the epidemiology. This review will examine how the nature, nurture (or the environment/exposome) and the microbiome play a complex role in deciphering the etiology of this debilitating condition, as the incidence rates have rapidly increased with industrialization and westernization in Asia, South America and the Middle East. The review also outlines the application of new biomedical engineering technologies, such as multi-omics profiling, computational modelling and microphysiologic systems, that are enabling systems-level study of host–microbe interactions in IBD and their use to inform precision medicine strategies for disease management. [30,31]

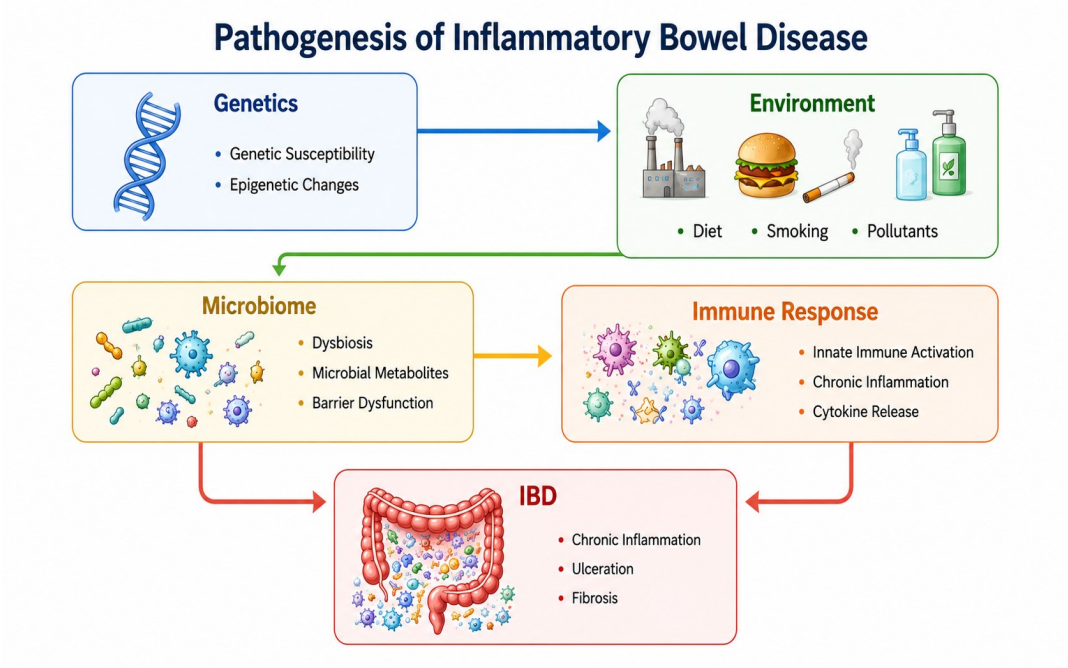


Figure 1. Systems-level framework of inflammatory bowel disease pathogenesis. The diagram shows that the response to all the factors involved in the development of inflammatory bowel disease (IBD) are interconnected. The composition and function of the gut microbiome are shaped by genetic predisposition and environmental factors like nutrition, antibiotics and lifestyle. Microbial dysbiosis breaks the integrity of guts and alters immune signaling pathway, resulting in the abnormal activation of innate and adaptive immune responses. All of these interactions contribute to the chronic inflammation and damage of the intestine seen in IBD. A systems-based view of these intricate host–environment–microbiome relationships will enable precision medicine strategies and analytical approaches based on biomedical engineering in research on IBD.

2. Nature: The Genetic Architecture

While IBD is not a classic Mendelian disorder, hereditary susceptibility is the strongest known risk factor. Genome-Wide Association Studies (GWAS) have revolutionized our understanding of IBD genetics, identifying over 240 susceptibility loci.[1,15,16]

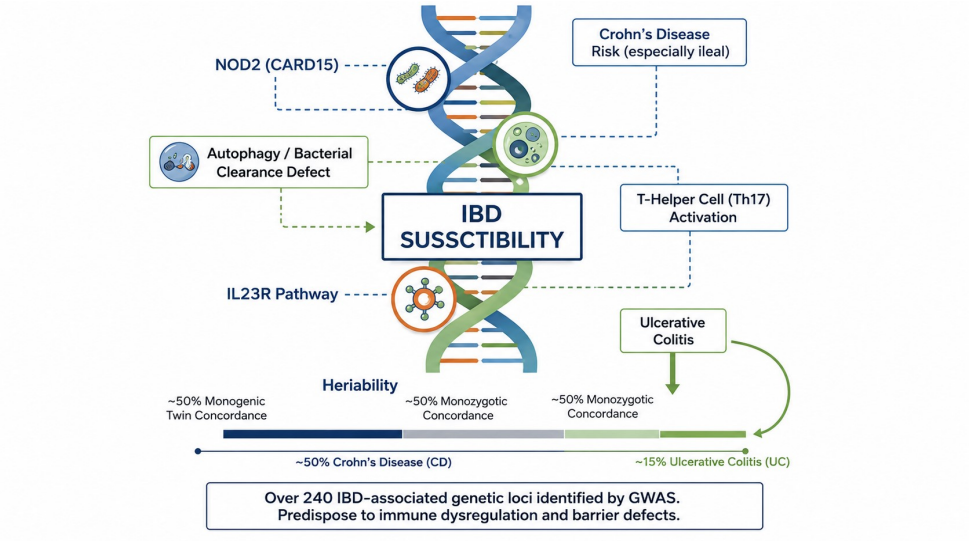


Fig. 2 The Genetic Architecture of cell

2.1 Key Susceptibility Loci

The first discovery of NOD2 mutations on chromosome 16 was a breakthrough in the research of IBDs. This gene encodes an intracellular sensor of the muramyl dipeptide in bacteria. Polymorphisms in NOD2 affect the host's ability to identify and eliminate bacteria and activate a hyperactive immune response as a countermeasure. This association is unique to Crohn's disease, especially ileal disease.

Autophagy Genes (ATG16L1, IRGM): Autophagy is the process of "recycling" of intracellular pathogens that is crucial for the cell. Mutations in ATG16L1 affect this process, leading to an abnormal ability of bacteria to survive inside intestinal cells and the development of chronic inflammation.

The genes in the IL23R pathway are shared risk factors for CD and UC, and suggest a role for Th17 cell mediated inflammation in the intestine [2,8]

2.2 Ethnicity and Heritability

Scrub the DNA and background for the sources of IBD, and you find that there are complicated patterns occurring among the various ancestries. Ethnic populations have also demonstrated varying susceptibility or "genetic loads" for the condition, with Ashkenazi Jewish populations having the highest susceptibility, up to four times that of other ethnic groups, indicating a higher concentration of risk alleles in this population. On the other hand, familial clustering is well established in Western populations, but less apparent in some Asian populations, although this difference is being closed down in the event of changing incidence rates around the world. [10,44,52] These patterns of hereditary transmission are best seen with twin studies (which provide a natural experiment for separating genetic influence from environmental exposure). Several studies have consistently shown that Crohn's disease (CD) has a greater genetic load than ulcerative colitis (UC). With identical (monozygotic) twins, who share 100% of their DNA, the concordance for CD is approximately 50%. The concordance rate for UC in identical twins is much lower, around 15%. This difference implies that genes might be important factors in the progression of Crohn's, but that external factors may be more important in the progression of ulcerative colitis. Arguably the most telling statistic, however, is that these numbers don't tell you. The concordance rate for identical twins would be in the vicinity of 100% if it was a genetic destiny. Identical twin pairs with a CD pro-band are discordant in one-half, and almost 85% of the pairs with UC are discordant, which is an irrefutable proof that genetics are not the only cause of the disease. The "heritability gap" strongly suggests that our DNA sets us up (loads the gun) but then some environment factors like diet, antibiotic use or certain microbial interactions pull the trigger and start pathogenesis [17,39,45].

3. Nurture: The Environmental Exposome

The environment provides the trigger, and the genes provide the power to the weapon. This realization has led to a shift in emphasis to the "exposome", which is the sum of all the biological effects of all environmental exposures experienced by an individual since conception. The argument for the exposome as a primary driver of Inflammatory Bowel Disease (IBD) is compelling because our genes do not evolve fast enough to explain the dramatic increase in the prevalence of IBD over the past 50 years all over the world. There is something in our contemporary way of living that is drastically changing our biological balance. [10,44,52]

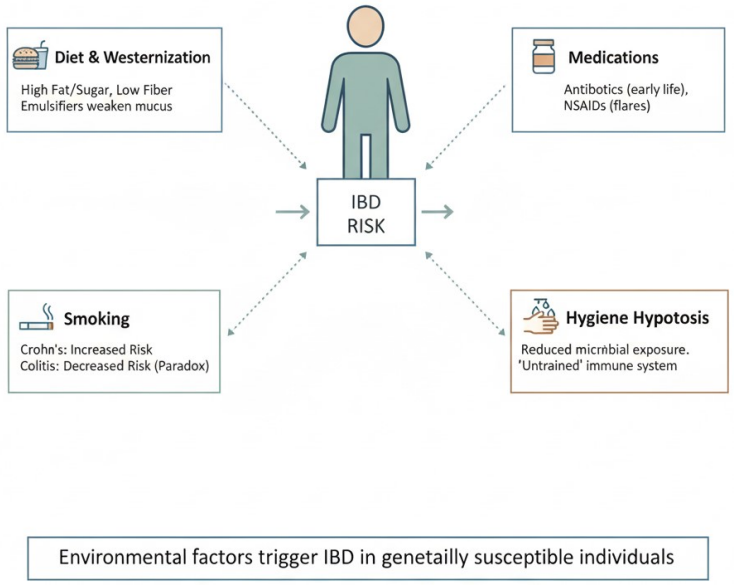


Fig. 3 The Environmental Exposome and its effects

3.1 Diet and Westernization

The The most widespread environmental change has been the “Western Diet”, the diet of excessive animal fat, refined sugars and ultra-processed foods, but, and this is the critical point, lacking in dietary fiber. This diet feeds the bad guys at the expense of the good guys, and provides direct chemical damage to the gut barrier in two ways, which is a "perfect storm" for developing inflammation. [17,22] Firstly, there's a disruption in a vital symbiotic process in the absence of fibre. Soluble fibre is the major fuel source for colonic bacteria which then break it down to produce Short-Chain Fatty Acids (SCFAs) including butyrate. Butyrate is not only a metabolite, it is the main energy source for colonocytes (colon cells) and an important regulator of immune homeostasis. A lack of fibre feeds these beneficial bacteria and they die, fewer butyrate are produced, the lining of the colon is starved and inflamed.[30,31,32]

Second, the food we use today has become different from what our gut evolved to eat, and, thus, processed with chemicals that were not present in the past. Dietary emulsifiers like polysorbate-80 and carboxymethylcellulose have been shown to be a risk in recent animal models. These agents are like detergents in the gut, breaking down the protective mucosal barrier which typically separates intestinal bacteria from the intestinal wall. After thinning of this mucus barrier bacteria can directly and abrasively come into contact with the epithelium and provoke an inflammatory response.[18,21]

3.2 Smoking: The IBD Paradox

One of the most baffling environmental triggers for IBD is cigarette smoking, which has a quite paradoxical association, depending on the specific type of IBD phenotype. [24,25] Smoking is definitely bad for Crohn's Disease (CD). It doubles the risk of developing the condition and also speeds up the onset of the condition. Smokers with CD tend to have a more aggressive clinical course, have to start immunosuppressive therapy earlier and have a much higher likelihood of surgical recurrence than non-smokers. Contrary to this, there is a confusing protective effect of smoking in Ulcerative Colitis (UC). Rarely do active smokers develop the disease and, a counterintuitive finding, the disease onset or flares tend to happen soon after quitting smoking. The mechanism continues to be studied but it is thought that nicotine promotes the production of mucus in the colon or affects the permeability of tight junctions, creating a false barrier in the colon. But with the systemic adverse effects of smoking, this "protective" role is of little therapeutic use.[24,26]

3.3 Hygiene and Early Life Exposures

The The ‘Hygiene Hypothesis' is a general one that can be used to explain the increased occurrence of autoimmune diseases in developed countries. It posits that the changes in sanitation, urbanization and fewer children in a household have reduced exposure to enteric pathogens and other microbes during childhood. If such challenges are not present, the developing immune system is not well "trained", and is unable to differentiate between harmless commensal organisms and dangerous invaders.[27] This effect is strongest regarding the use of antibiotics. Giving antibiotics in the first year of life has consistently been linked to an increased risk for pediatric IBD. Antibiotics disrupt the natural balance of the microbial community, potentially for life, by eliminating the developing microbial community during a critical window in immune system maturation—making microbial imprinting a permanent possibility.Antibiotics have a time window for immune system maturation when they can alter the ecology of the gut for a lifetime by killing off the developing community of microbes.

4. The Microbiome: The Missing Link

The gut microbiome is the construction team; if the blueprint is the genes and the materials are the environment. The relationship in IBD is considered a dysbiosis: a functional and compositional disruption of the gut ecosystem that disrupts a symbiotic relationship to become pathogenic. [30,39]

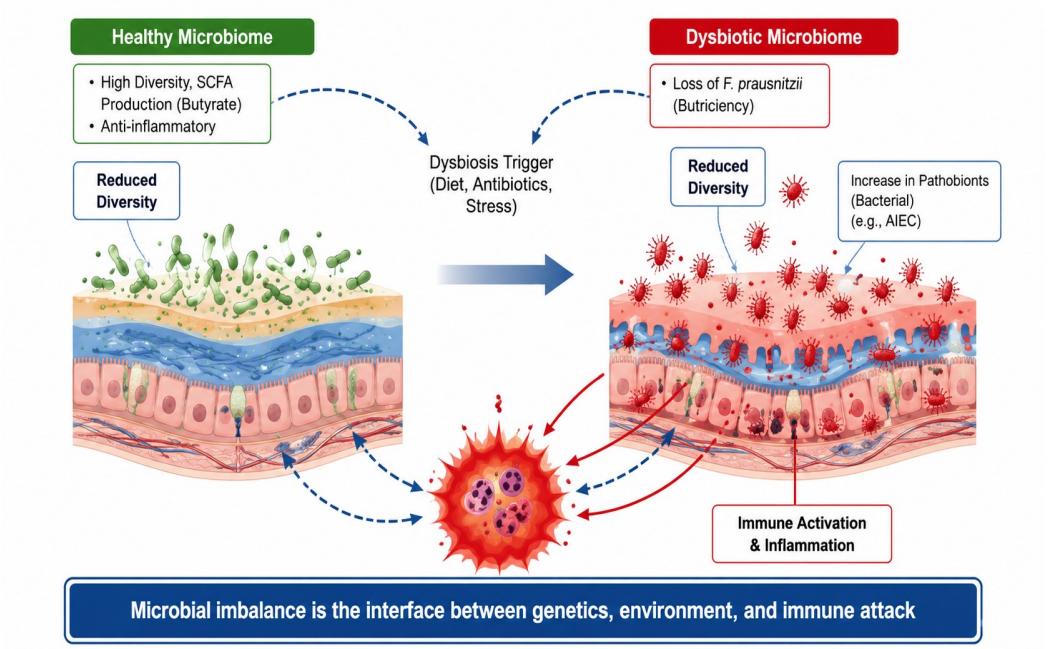


Figure 4. Systems-level interaction between host genetics, environmental exposures, gut microbiome composition, and immune signaling pathways contributing to inflammatory bowel disease.

4.1 Loss of Diversity

One common feature of all the IBD cohorts is the substantial decrease in alpha-diversity. In healthy gut the microbial species are like a lush rainforest, while in IBD, it is more like a monoculture. This "ecological collapse" makes it harder for the microbiome to withstand stressful conditions, and leaves room for opportunistic pathogens to proliferate when they would normally be kept under control by a diverse community of microorganisms. [30,31]

4.2 "Good" vs. "Bad" Bacteria

This change is more than a mere number, it's about players. The dysbiosis of IBD is an "changing of the guard" with two key groups: A significant decrease of the phylum Firmicutes, particularly of *Faecalibacterium prausnitzii*. An important "peacemaker" in the gut, producing butyrate and secreting anti-inflammatory proteins. Without it, there is a natural brake on inflammation that is removed. [32,33,34] The Proteobacteria invade the void, the Rise of Pathobionts. One of the outstanding examples is the Adherent-Invasive Escherichia coli (AIEC). AIEC has the ability to attach to and penetrate the enterocytes, while other normal flora float in the lumen. It can even live and multiply within macrophages, the cells whose job it is to kill it off, and force them to spew out pro-inflammatory cytokines such as TNF-alpha. [35,36]

5. Immunological Dysregulation

Host immune response against the intestinal microbial dysbiosis and the contributions of genetic susceptibility and environmental insults is the final common pathway leading to destruction of intestinal tissue. It usually starts with a barrier defect, called the "Leaky Gut. The causes of this increased intestinal permeability can be either genetic or environmental (such as the emulsifiers mentioned earlier) and make it easier for antigens and bacteria in the gut to enter the lamina propria, the tissue beneath the gut lining. If the barrier is broken, the immune response breaks down in two phases. Innate Immune System (Macrophages and Dendritic cells) is incapable of efficiently clearing the invading bacteria, sometimes due to genetic defects in the proteins that detect bacteria, such as NOD2, or those that control the process of autophagy, such as ATG16L1. [4,6,37,39] This failure leads to a hyperactive, exaggerated immune response, or overshooting immune overreaction, in compensation. T-cells recruited in area; release cytokine storm. In Crohn's disease, however, Th1 and Th17 cells around the site produce the cytokines that cause this response, such as TNF-alpha, IL-12, and IL-23. In the case of Ulcerative Colitis, the reaction is more Th2-like (but not the same as classic allergy pathways). This constant production of pro-

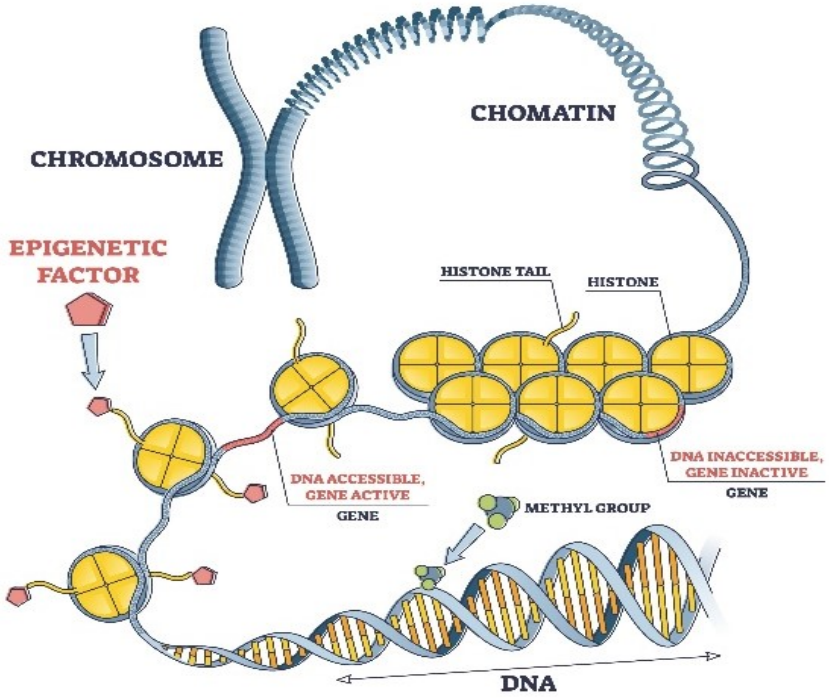
inflammatory cytokines creates a vicious cycle of tissue damage, ulceration and fibrosis which is the clinical reality of IBD [2,5,38]

6. Epigenetics: Bridging Nature and Nurture

In the battle between genetics and environment, epigenetics is the place where they meet. Describes "heritability gap". Chemical changes to the genome that modify gene expression without changing the actual gene sequence are known as epigenetic marks and can be "left" on the genome by environmental factors.

6.1 DNA Methylation and Histone Modification

DNA methylation is the most well studied epigenetic mechanism in IBD. Comparisons of discordant monozygotic twins (one twin with IBD and the other without) have shown that the twins have distinct methylation profiles with significant differences observed in methylation at loci linked to immune regulation. The Mechanism: Environmental stressors – like smoking, or inflammation – can put methyl groups on parts of DNA, kind of "silencing" genes that stop inflammation. Or, histone proteins can be acetylated, which "opens up" DNA and leads to an overexpression of inflammatory cytokines. Clinical Evidence: Different methylation patterns have been seen in the intestinal epithelial cells of people with IBD compared to healthy people. Importantly, some of these changes seem to be reversible, indicating that therapeutic interventions might be able to "reset" the epigenetic landscape.[40,42]



Fig, 5 Epigenetic Mechanism of the cell

6.2 MicroRNAs (miRNAs)

MicroRNAs are small non-coding RNAs, which function as post-transcriptional regulators – essentially as volume knobs for gene expression. Dysregulation of specific miRNAs (e.g., miR-192 and miR-21) has been observed in IBD. These molecules can act unintentionally as inhibitors of protein translation which is necessary for the integrity of the intestine, making the "Leaky Gut" a direct link to the gene regulation.

7. Therapeutic Horizons: Targeting the Cause

The multi-factorial pathogenesis of IBD is changing the course of treatment from symptom control to precision medicine based on targeting specific pathogenic pathways.

7.1 Biologics and Small Molecules

New medical treatments directly target the Immunological Dysregulation. Anti-TNF Agents: These drugs block the overproduction of Tumor Necrosis Factor (TNF-alpha) by the overactive adaptive immune system. Leukocyte Trafficking Inhibitors: These drugs (like vedolizumab) block the homing of T-cells to the gut tissue, which targets the site of the inflammation and decreases systemic effects. • JAK inhibitors: Small molecules which block intracellular signalling pathways and prevent the ‘production order' for inflammatory cytokines from being carried out. [46,47,48]

7.2 Microbiome-Based Therapies

Ecological balance is one of the major fields of study as Dysbiosis plays a central role. Fecal Microbiota Transplantation (FMT): Although highly effective for C. difficile infection, FMT in IBD (especially UC) has had mixed, but promising, outcomes. The idea is to 're-seed' the gut with a rich, healthy microbial community. Precision Probiotics: Going beyond generic probiotics, the next-generation of probiotics are designed to re-introduce missing keystones, such as *Faecalibacterium prausnitzii*, to restore butyrate production and mucosal healing, respectively.[49,50,51]

7.3 Dietary Interventions

The Environmental Exposome targets using food as medicine. Exclusive Enteral Nutrition (EEN): In children with Crohn's disease, EEN can achieve remission in 6-8 weeks which is as effective as steroid therapy, when solid food is omitted. This likely does this by limiting pathobionts, eliminating antigens in the diet (such as emulsifiers) and permitting the mucosal barrier to rest and repair.

8. Biomedical Engineering Approaches in IBD Research

New techniques in biomedical engineering greatly broadened the range of tools available to study the complex pathogenesis of inflammatory bowel disease (IBD). Given that IBD is a multifactorial disease, involving interactions between the host genome, the environment, immune responses and the gut microbiome, engineering-driven analytical platforms offer useful tools to investigate these complex systems at various biological levels. By leveraging technologies like multi-omics analysis, computational modeling, systems using organs-on-chips, and biosensors diagnostics, researchers can gain deeper insights into the mechanisms underlying disease and inform the creation of personalized therapeutic approaches.

The biomedical engineering technologies for systems-level investigation of inflammatory bowel disease (IBD) will be utilized. This figure depicts the advanced biomedical engineering tools that enhance understanding of the pathogenesis of IBD. Multi-omics technologies (genomics, transcriptomics, proteomics, and metabolomics) allow for an in-depth characterization of the host–microbiome interactions. Computational modeling and bioinformatics analysis are methods that combine enormous biological data to uncover disease-associated networks and forecast disease progression. Microphysiological systems like gut-on-chip models provide controlled environment to model intestinal microenvironment for epithelial barrier function and interactions with the microbial community. A set of biosensor technologies could detect markers of inflammation, microbial metabolites, and intestinal permeability markers, providing real-time monitoring of the disease activity. These technologies can be used together to offer a systems-level approach to understanding the mechanism of action of IBD and precision medicine strategies.

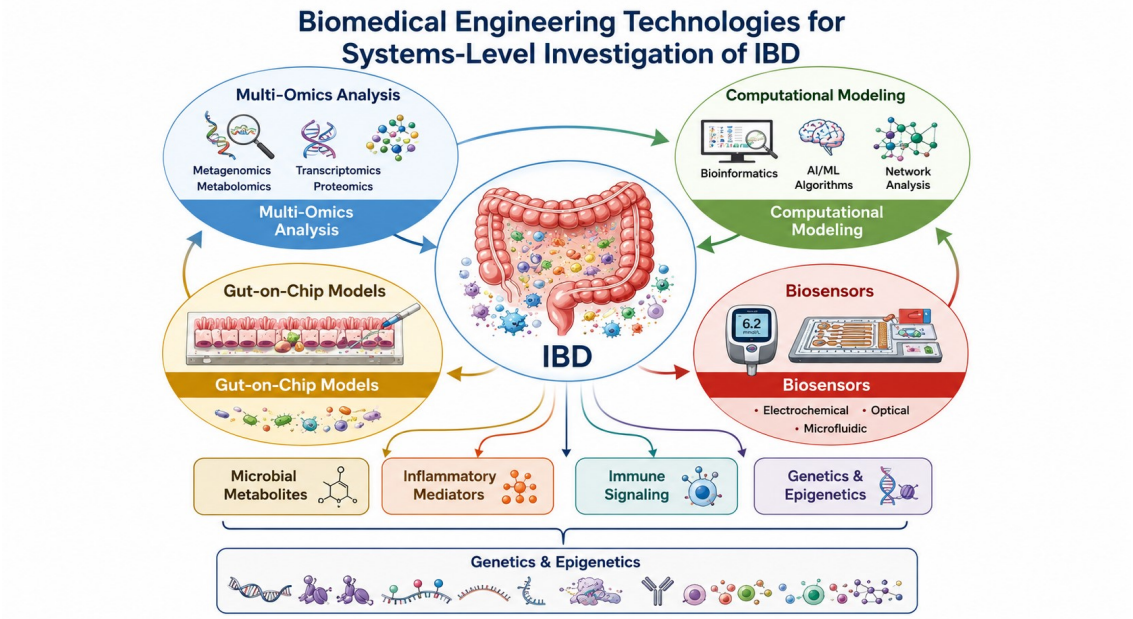


Figure 6. Biomedical engineering technologies for systems-level investigation of inflammatory bowel disease (IBD)

8.1 Multi-Omics Technologies

Characterizing the molecular and microbial environment of IBD has become necessary and has been made possible by multi-omics approaches. New high throughput sequencing technologies like metagenomics and metatranscriptomics allow the characterization of gut microbial communities and the functional gene expression profiles. Complementary techniques like metabolomics and proteomics enable identification of microbial metabolites, inflammatory mediators, and signaling molecules that play a role in intestinal

homeostasis and inflammation. Combination of genomic, transcriptomic, proteomic, and metabolomic data can give researchers a comprehensive systems-level models of host–microbiome interactions that help with the onset and progression of disease. They provide a valuable integrative analysis to help pinpoint the possible diagnostic biomarkers and therapeutic targets for precision medicine in IBD. [54,55]

8.2 Bioinformatics and Computational Modeling

The large amounts of data collected by multi-omics technologies demand sophisticated computational and bioinformatics analysis for elucidation. More and more, network-based computational models are employed to study interactions among host genetic susceptibility loci, microbial species and immune signaling pathways. Using machine learning algorithms and artificial intelligence applications, there has also been work predicting disease risk, classification of disease phenotypes, and the identification of potential disease treatment responses according to the composition of the microbiome and the molecular characteristics of the host. These computational systems enable researchers to shift the paradigm from simple factor analysis to development of a systems biology understanding of the pathogenesis of IBD. [57,60]

8.3 Microphysiological Systems and Gut-on-Chip Models

Microfluidic organ-on-chip technologies have become a powerful experimental tool to investigate intestinal physiology and host–microbiome interactions. Gut-on-chip models emulate important characteristics of the intestinal microenvironment, such as characteristics of the epithelial barriers, peristaltic motion, and microbial colonization. These platforms provide live microscopy of epithelial responses to microbial communities, inflammatory mediators and pharmacological agents in a controlled environment. These offer useful alternatives to traditional animal models and help to more accurately reflect intestinal barrier function, immune signaling, and microbial dysbiosis in IBD. [54]

8.4 Biosensors and Biomarker Monitoring

Biosensor technologies have also been developed with the help of biomedical engineering, which are able to identify biomarkers linked to inflammation in the intestines. Biosensors of electrochemical, optical and microfluidic design have been created to analyze biological samples for inflammatory cytokines, microbial metabolites and intestinal permeability markers. These technologies have potential to enable rapid (non-invasive) monitoring of disease activity and therapeutic response. Wearable or implantable biosensor systems and systems that can monitor inflammatory markers continuously could also enable early detection of a flare up of disease and aid disease management in the future. [55,56] Together, these biomedical engineering solutions will enable innovative tools to probe the multifactorial mechanisms of inflammatory bowel disease. The combination of engineering technologies, microbiology, and clinical research and clinical trials will be key to improving precision medicine approaches and therapeutic interventions for IBD. [59]

9. Conclusion:

IBD is not caused by a single problem in the system, but is caused by a failure of a safety net. It's caused by a “perfect storm” of a genetically predisposed host with certain polymorphisms in bacterial sensing or barrier function, and an environment that is becoming more hostile for gut health at the modern time. Westernisation of diet and lifestyle leads to changes in the microbiome, which eliminates beneficial species and promotes the proliferation of invasive pathobionts. This ecological change is a dynamic that plays into the host's immune system which is already primed by the genetic and epigenetic process to attack the intestinal tissue in an unrelenting way. To understand the causes of IBD, we need to consider a whole landscape and recognize that everyone's genome interacts with their diet and the trillions of microbes that they host in a two-way street. There is no 'one size fits all' cure for IBD, but there are personalized strategies that will take down this pathogenic web of disease, one link at a time.

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