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A SYSTEMIC REVIEW ON THE PATHOGENESIS OF IBD, ALTERATIONS IN GUT MICROBIAL ECOLOGY OBSERVED IN IBD, ROLE OF CYTOKINES (TNF-, INF-, IL-1, IL-6, IL-4, IL-5, IL-10) IN IBD AND RECENT THERAPEUTIC STRATEGIES

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ABSTRACT: Inflammatory bowel disease (IBD) is a chronic inflammatory illness of the gastrointestinal tract that consists of Crohn's disease and ulcerative colitis. The pathogenesis of IBD is multifactorial and involves a complex interplay between genetic, environmental, and immunological factors. A comprehensive literature search was conducted using relevant databases, such as PubMed, Scopus, and Web of Science. A tool such as PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) ensures that the review is conducted systematically and transparently. Alterations in gut microbial ecology are a hallmark of IBD and include decreased microbial diversity, an expansion of potentially harmful bacteria, and a loss of beneficial bacteria. These alterations are thought to contribute to the dysregulated immune response observed in IBD. The current understanding of the pathogenesis of IBD suggests that a dysregulated immune response to commensal bacteria in the gut plays a central role in the development and progression of the disease. Alterations in gut microbial ecology are a hallmark of IBD and include decreased microbial diversity, an expansion of potentially harmful bacteria, and a loss of beneficial bacteria. These alterations in the gut microbiota are thought to contribute to the dysregulated immune response observed in IBD.

INTRODUCTION: Inflammatory bowel disease (IBD) is a chronic inflammatory illness of the gastrointestinal tract that consists of Crohn's disease and ulcerative colitis. The pathogenesis of IBD is multifactorial and involves a complex interplay between genetic, environmental, and immunological factors [1]. Recent studies have identified alterations in gut microbial ecology, including dysbiosis, as a key factor in the development and progression of IBD. The gut microbiome is a complex ecosystem of

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microorganisms that play important roles in host metabolism, immune function, and protection against pathogens [2]. Dysbiosis, characterized by changes in the composition and function of the gut microbiome, is commonly observed in IBD patients. These alterations in gut microbial ecology have been linked to changes in immune function and the development of chronic inflammation [3]. Cytokines, including TNF-, INF-, IL-1, IL-6, IL-4, IL-5, and IL-10, are key regulators of the immune response and play important roles in the pathogenesis of IBD [4]. Dysregulation of cytokine signaling pathways has been implicated in the development and progression of IBD. Recent therapeutic strategies for IBD have focused on targeting cytokine pathways to modulate the immune response and reduce inflammation [5]. In this review, we will provide an overview of the pathogenesis of IBD, the alterations in gut microbial ecology observed in IBD, and the role of cytokines in IBD. We will also discuss recent therapeutic strategies for IBD, including cytokine-targeted therapies. Through this review, we aim to provide a comprehensive understanding of the current state of knowledge on IBD pathogenesis and potential therapeutic interventions.

IBD is a chronic and debilitating illness that affects 2.5 million people of European descent, but its occurrence is increasing in Central and East Asian populations, who are now considered newly industrialized countries [6]. Non-European populations have unique phenotypic traits for IBD. For example, Asians with Crohn's disease (CD) and Ulcerative colitis (UC) have lower rates of family history and extra-intestinal manifestations compared to Europeans. In CD, Asians show a higher incidence among males, stricter disease, and more perianal involvement compared to Europeans. On the other hand, in UC, Asians have lower rates of extensive colitis and colectomy compared to Europeans [7].

Role of cytokines in IBD: The intestinal immune system's major signaling molecules, cytokines, are also understood to contribute to the destabilization of the normal state of controlled inflammation (physiological inflammation of the gut). Small peptide proteins described as cytokines are mostly produced by immune cells and help cells respond, encourage the proliferation of antigen-specific effector cells, and mediate both local and global inflammation through autocrine, paracrine, and endocrine pathways. The innate immune response is essential in IBD [8]. A variety of cytokines is produced by macrophages and activated dendritic cells (DC) that actively control the inflammatory response in UC and CD. When these antigen presentation cells (APC) secrete them, the cytokines that result stimulate and differentiate a large number of T cells, so triggering the adaptive immune response.IBD is compounded by the cumulative influence of APCs, Th1, Th2, T regulatory cells, and most formally named Th17 and their cytokine products. As demonstrated in **Table 1**, both lengthy cytokines (such as TNF-, INF-, IL-1, IL-6, IL-4, IL-5, IL-10, and TGF-) and newly described cytokines (like IL-13, IL-12, IL-18, and IL-23) that have been thought to be either pro- or anti-inflammatory affect these cellular interactions [9]. Although cytokines mediate a range of common responses in IBD, along with the regulation of the output of inflammatory mediators, reactive oxygen metabolites, nitric oxide, leukotrienes, platelet-activating factor, and prostaglandins, in addition to the activation of the nuclear factor B (NF-B) and inhibition of apoptosis, how cytokines determine the nature of the immune response in IBD may differ substantially between IBD forms [10].

TABLE 1: THE SIGNIFICANCE OF CYTOKINES AND THE CELL LINES INVOLVED IN THEIR SYNTHESIS IN PATIENTS WITH IBD

Cytokine	Ulcerative Collitis	Crohn's Disease	Cells involved in the Production
TNF-α	Upregulated	Upregulated	Macrophages
TL1α	Unknown	Upregulated	Th1
IL-1β	IL-1ratio	IL-1ratio	Macrophages
IL-6	Upregulated	Upregulated	DC,Th17&others
IL-18	Not	Yes	Macrophages
TGF-β	May be defective signaling	Not Clear	Th-0,Th-3,T-reg
IL-10	Not clear	Yes	Tr1
IL-4	Not Clear	Not Clear	Th2
IL-12	Upregulated	Upregulated	Macrophages

IL-23	Yes	Yes	DC
IL-27	Not clear	Upregulated	APCs
IL-17	Upregulated	Upregulated	Th17
IL-13	Upregulated	Not	NK
IL-5	Upregulated	Not	Th2

A critical element in regulating the immune response is played by the lymphocyte subtype known as Th cells. They assist in determining the specificity of antibodies generated by B-cells and activating other immune cells. A Th cell differentiates into Th1 cells, Th2 cells, or additional Th lineages after multiplying. As seen in **Fig. 2**, Th1 cells play a role in cell-mediated immunity that results in the production of pro-inflammatory cytokines such as interferon-gamma (IFN-γ), TNF-, and interleukin (IL)-2. IL-4, IL-5, IL-6, and IL-10 are examples of anti-inflammatory cytokines that are produced by Th2 cells and are part of the humoral immune response [11]. Th1 and Th2 lymphocytes collaborate to produce more Th1 cells while suppressing the growth of Th2 cells. On the other hand, Th2 cytokines promote Th2 cell production in addition to suppressing Th1 cells. The ratio of Th2 to Th1 cells is equal under normal circumstances [12]. A polarised type 1 immune response that results in continuous gut inflammation is significantly linked to the emergence of immunological-mediated diseases like Crohn's disease.

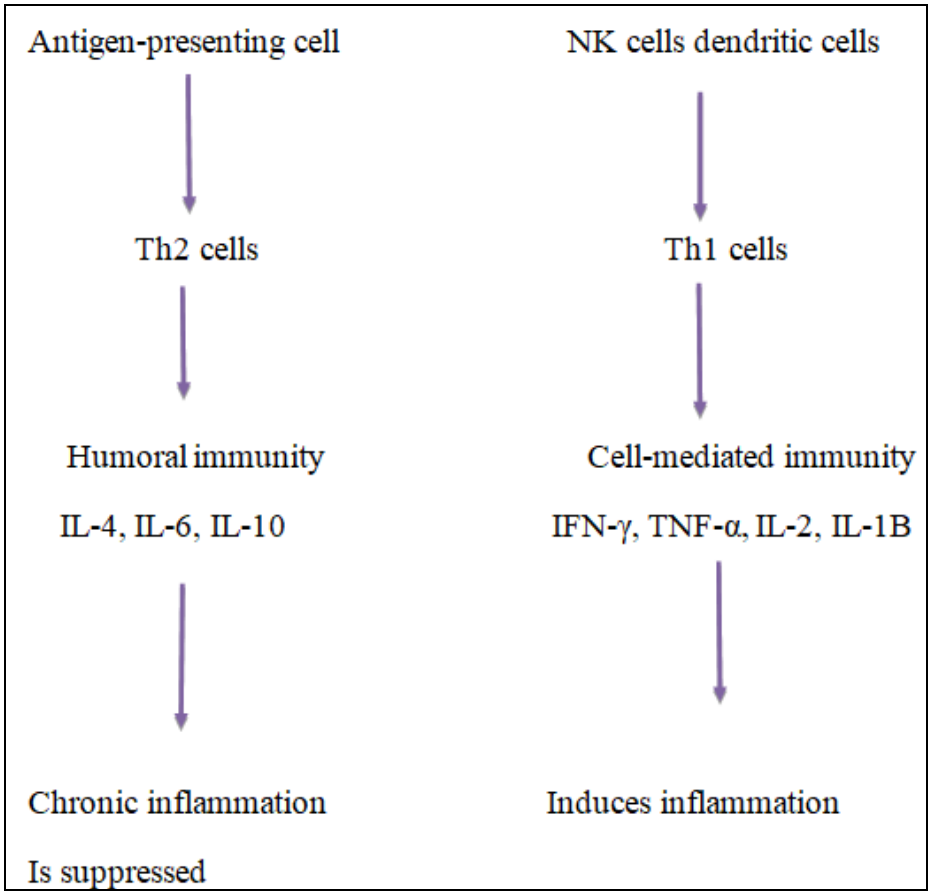

FIG. 1: FACTOR INFLUENCING T-LYMPHOCYTES DIFFERENTIAL IN IBD

METHODOLOGY:

Conduction of a Literature Search: A comprehensive literature search was conducted using relevant databases, such as PubMed, Scopus, and Web of Science. Use keywords related to the research question, such as "pathogenesis of IBD," "gut microbial ecology in IBD," "cytokines in IBD," and "therapeutic strategies for IBD." It is also helpful to include relevant subtopics such as "immunology," "genetics," and "epidemiology."

Screen and Select Relevant Studies: the titles and abstracts of the retrieved studies were reviewed to identify relevant articles. The studies were

excluded that do not meet the inclusion criteria, such as studies that are not in English or do not focus on human subjects.

Read and Analysing the Selected Studies: The selected studies and extract relevant data was used in a standardized form. Tool such as PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) is used to ensure that the review is conducted in a systematic and transparent manner.

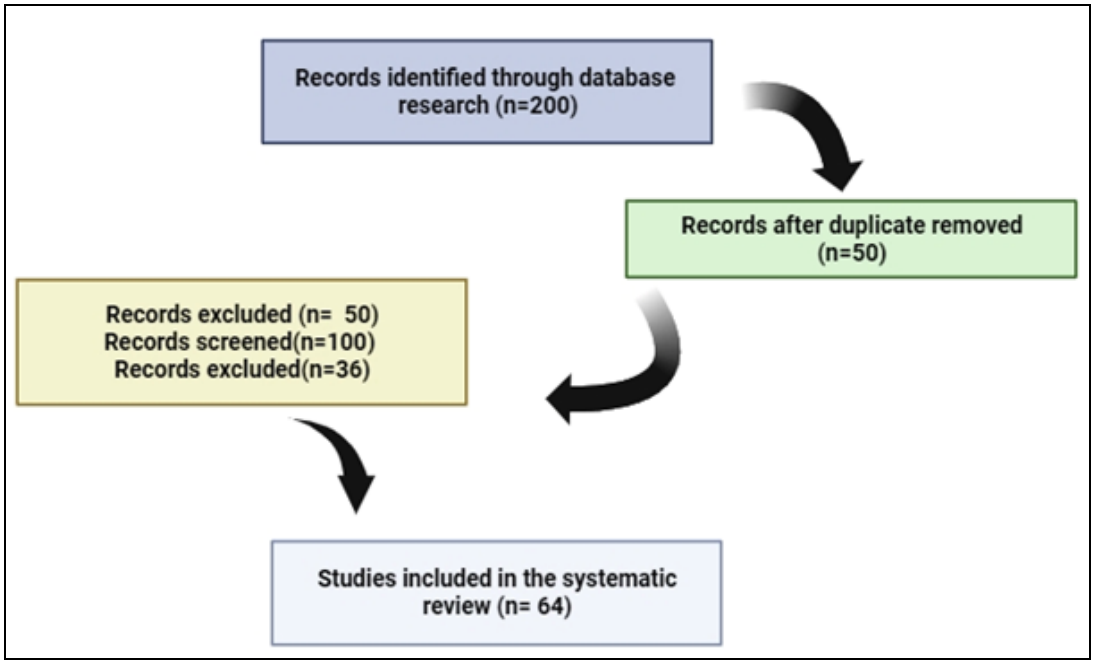

FIG. 2: PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES (PRISMA) STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

TABLE 2: SCIENTISTS AND THEIR WORK IN IBD FROM PAST TO RECENT ADVANCEMENT (INFLAMMATORY BOWEL SYNDROME)

Area of Research	Scientist	Contributions
Pathogenesis of IBD	Dr. Burrill Crohn	First to describe Crohn's disease
	Dr. David Sachar	Proposed concept of "leaky gut" in IBD
	Dr. Jean-Frederic Colombel	Contributed to identification of genetic factors associated with IBD
Alterations in gut microbial ecology observed in IBD	Dr. Jeffrey Gordon	Pioneer in the field of gut micro biome research
	Dr. Dan Knights	Conducted research on microbial ecology of IBD
Role of cytokines in IBD	Dr. Charles Dinarello	Leading expert on role of IL-1 in inflammatory diseases, including IBD
	Dr. Stephen Hanauer	Conducted numerous studies on role of TNF-α in IBD
Recent therapeutic strategies	Dr. Mark Pimentel	Developed rifaximin, an antibiotic that targets small intestinal bacterial overgrowth
	Dr. William Sandborn	Conducted numerous clinical trials of biologic therapies for IBD
	Dr. Scott Plevy	Conducted research on role of gut micro biota in IBD and involved in development of micro biome-based therapies for the disease

Pathogenesis of IBD: Dr. Burrill Crohn was an American gastroenterologist who was the first to describe Crohn's disease, which is a chronic inflammatory condition that affects the digestive system.IBD etiology is complicated **Fig. 1** and unknown in many ways. In 1932, along with his colleagues Dr. Leon Ginzburg and Dr. Gordon D. Oppenheimer, Dr. Crohn published a landmark paper in the medical journal Gastroenterology describing a series of patients with chronic inflammation of the terminal ileum, the last part of the small intestine that did not fit the diagnostic criteria of either ulcerative colitis or tuberculosis [13].

Crohn and his colleagues named this new condition "regional ileitis," but it later became known as Crohn's disease in honour of its discoverer. The paper was based on the clinical observation of 14 patients, and it included detailed descriptions of the disease's symptoms, pathology, and radiological findings [14]. Dr. Crohn's subsequent research focused on the clinical features and management of Crohn's disease, and he is credited with developing the first effective medical treatment for the disease. He also made significant contributions to the understanding of other gastrointestinal disorders, such as diverticulitis and inflammatory bowel disease. Dr. Burrill Crohn's ground-breaking work on Crohn's disease has had a significant impact on the diagnosis and treatment of the disease, and his legacy continues to influence gastroenterology and medical research to this day [15].

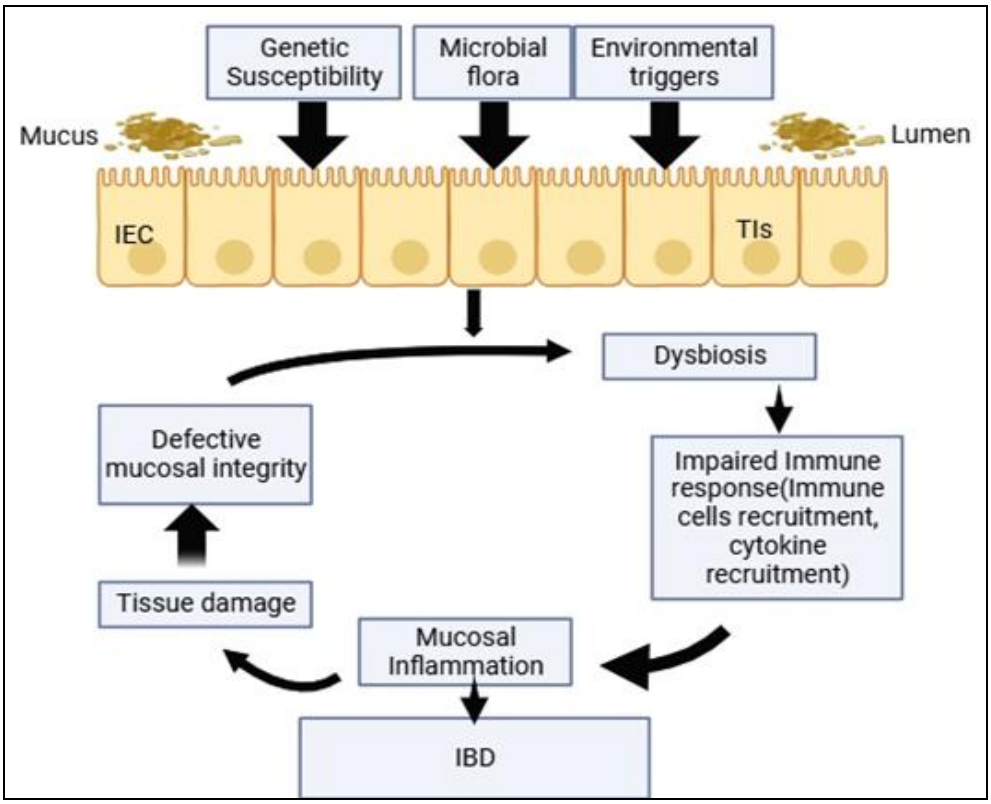

FIG. 1: ILLUSTRATION OF THE IBD ETIOLOGY AND THE ROLE OF ENVIRONMENTAL VARIABLES IN INTESTINAL BARRIER DISRUPTION IEC STAND FOR INTESTINAL EPITHELIAL CELLS TJ TIGHT JUNCTION

Dr. David Sachar Proposed concept of "Leaky gut" in IBD: Dr. David Sachar was an American gastroenterologist who proposed the concept of "leaky gut" in the development of inflammatory bowel disease (IBD). The theory suggests that increased intestinal permeability allows bacteria and toxins to escape from the gut into the bloodstream, triggering an immune response that leads to chronic inflammation [16]. In 1988, Dr. Sachar and his colleagues published a study in the journal Gut that examined the prevalence of increased intestinal permeability in patients with Crohn's disease and ulcerative colitis. The study found that patients with active IBD had significantly higher levels of intestinal permeability than healthy controls, suggesting that increased permeability may play a role in the pathogenesis of IBD. Since then, numerous studies have investigated the relationship between intestinal permeability and IBD, with conflicting results [17- 18]. Some studies have supported the leaky gut hypothesis, while others have found no significant association between intestinal permeability and IBD.

However, recent research has suggested that changes in the gut micro biome and gut barrier function may be important factors in the development and progression of IBD [19- 20]. For example, a 2018 study published in the journal Nature found that certain bacteria in the gut can increase intestinal permeability and trigger

inflammation in mice with IBD [21]. Overall, the role of intestinal permeability in the pathogenesis of IBD remains a topic of on-going research and debate. While the leaky gut hypothesis has not been definitively proven, it has generated significant interest and has led to further investigation into the complex interplay between gut microbiota, gut barrier function, and immune response in IBD.

Dr. Jean-Frederic Colombel Contributed to Identification of Genetic factors Associated with IBD: Dr. Jean-Frederic Colombel is a French gastroenterologist who has made significant contributions to the identification of genetic factors associated with inflammatory bowel disease (IBD). In 2001, Dr. Colombel and his colleagues published a study in the journal Nature Genetics that identified a gene called NOD2 as a major susceptibility gene for Crohn's disease [22]. This discovery was a significant step forward in understanding the genetic foundation of IBD, and it provided the way for more study into the complex genetic components that contribute to the disease's genesis and progression. Since then, Dr. Colombel has been involved in numerous studies investigating the genetics of IBD, including genome-wide association studies (GWAS) and meta-analyses of genetic data from large cohorts of patients with Crohn's disease and ulcerative colitis. His research has identified several other genes that are associated with IBD, including IL23R, ATG16L1, and IRGM [23]. Dr. Colombel has also been involved in clinical trials of new treatments for IBD, and he has been a strong advocate for personalized medicine approaches to the management of the disease. His work has had a significant impact on the field of gastroenterology and has helped to improve our understanding of the genetic and biological mechanisms underlying IBD.

Alterations in Gut Microbial Ecology Observed in IBD Dr. Jeffrey Gordon Pioneer in the field of Gut Micro Biome Research: Dr. Jeffrey Gordon's research has made significant contributions to our understanding of the gut micro biome and its role in health and disease, particularly in inflammatory bowel disease (IBD). His work has shown that there are significant microbial imbalances in the gut of individuals with IBD, and that these imbalances can contribute to the development and progression of the disease [24]. One key conclusion from his research is that the gut micro biome plays a critical role in maintaining the health of the digestive system [25]. When there is a disruption in the balance of microbes in the gut, this can lead to inflammation and damage to the intestinal lining, which can contribute to the development of IBD. Another important conclusion is that there is a need for personalized approaches to treating IBD that take into account the unique microbial communities present in each patient's gut [25]. By understanding the specific microbial imbalances that are contributing to a patient's symptoms, it may be possible to develop targeted therapies that restore balance to the gut micro biome and improve outcomes for individuals with IBD.

Overall, Dr. Gordon's research highlights the importance of the gut micro biome in the development and progression of IBD and underscores the need for further study and personalized approaches to treatment. His work has opened up new avenues for developing effective therapies for this complex and debilitating disease.

Dr. Dan Knights Conducted Research on Microbial Ecology of IBD: Dr. Dan Knights is another prominent researcher who has conducted research on the microbial ecology of inflammatory bowel disease (IBD). Dr. Knights' research focuses on using computational tools to study the human microbiome and its relationship to health and disease, with a particular emphasis on IBD. His research has shown that there are significant differences in the microbial communities present in the gut of individuals with IBD compared to healthy individuals, and that these differences are associated with changes in the metabolic and functional properties of the microbiome. One of Dr. Knights' key contributions has been the development of new computational tools and techniques for analysing microbial communities [26]. For example, he has developed a method called "MaAsLin" (Multivariate Association with Linear Models) that allows researchers to identify specific microbial species or functional pathways that are associated with a particular disease or condition [27]. Overall, Dr. Knights' research has advanced our understanding of the microbial ecology of IBD and has opened up new avenues for developing personalized approaches to treatment.

His work highlights the importance of using computational tools and techniques to study the complex relationships between the gut microbiome, the host immune system, and the development of disease.

Role of cytokines in IBD Dr. Charles Dinarello Leading Expert on role of IL-1 in Inflammatory diseases, including IBD: Dr. Charles Dinarello is a leading expert on the role of cytokines, particularly interleukin-1 (IL-1), in inflammatory diseases, including inflammatory bowel disease (IBD). His research has shown that cytokines such as IL-1 play a critical role in the development and progression of IBD [28]. These cytokines are produced by immune cells in the gut in response to microbial stimuli and can activate other immune cells, leading to chronic inflammation and tissue damage. One of key contributions to the field has been the development of therapies targeting IL-1 and other cytokines as a treatment for inflammatory diseases, including IBD [28]. For example, he was involved in the development of an IL-1 receptor antagonist (anakinra), which has shown promise in clinical trials for the treatment of Crohn's disease [29].

Overall, Dr. Dinarello's research highlights the central role of cytokines in the development and progression of IBD, and underscores the potential of targeting these cytokines as a therapeutic approach. His work has opened up new avenues for developing more effective treatments for this complex and challenging disease.

Dr. Stephen Hanauer Conducted Numerous Studies on Role of TNF-α in IBD: Dr. Hanauer's research has demonstrated that TNF-α plays a key role in the pathogenesis of IBD, particularly in Crohn's disease. TNF-α is a pro-inflammatory cytokine that is produced by immune cells in the gut and can cause damage to the intestinal mucosa. By blocking TNF-α, it is possible to reduce inflammation and improve symptoms in patients with IBD [30]. Dr. Hanauer has been involved in the development of several biologic therapies that target TNF-α, including infliximab, adalimumab, and certolizumab pegol. These therapies have been shown to be effective in inducing and maintaining remission in patients with moderate to severe Crohn's disease and ulcerative colitis.Infliximab, adalimumab, and certolizumab pegol are examples of biologic therapies that target TNF-α and are used to treat inflammatory bowel disease (IBD) [31]. Infliximab and adalimumab are both monoclonal antibodies that bind to TNF-α and block its activity [32]. They are used to treat moderate to severe Crohn's disease and ulcerative colitis that have not responded to conventional therapies such as corticosteroids and immunomodulators [33]. These drugs are administered via injection or infusion and can induce and maintain remission in a significant proportion of patients with IBD.

Certolizumab pegol is a newer biologic therapy that also targets TNF-α. It is a pegylated Fab fragment of a monoclonal antibody that binds to TNF-α and prevents it from binding to its receptors [34]. Like infliximab and adalimumab, certolizumab pegol is used to treat moderate to severe Crohn's disease and ulcerative colitis that have not responded to other therapies. It is administered via subcutaneous injection. While these biologic therapies have been shown to be effective in treating IBD, they can also have side effects such as increased risk of infections and allergic reactions [35]. Close monitoring is necessary to ensure that patients receive the appropriate dose and duration of therapy.

Overall, Dr. Hanauer's research has greatly advanced our understanding of the role of TNF-α in IBD and has led to the development of new and effective treatments for this complex and challenging disease. His work has been instrumental in improving the lives of millions of individuals living with IBD.

Dr. Scott Plevy Conducted Research on Role of Gut Micro Biota in IBD and involved in Development of Micro Biome-based Therapies for the disease: One of Dr. Plevy's main research interests is the use of microbiome-based therapies for IBD. The gut microbiota is a complex community of microorganisms that play a crucial role in maintaining the health of the digestive system. In IBD, there is an imbalance in the gut microbiota that leads to chronic inflammation and damage to the intestinal lining. Dr. Plevy's research has focused on developing therapies that target the gut microbiota to restore balance and reduce inflammation in IBD [36]. He has been involved in clinical trials of several microbiome-based

therapies, including faecal microbiota transplantation (FMT) and microbial bio therapeutic products (MBPs). FMT involves the transfer of faecal matter from a healthy donor to a patient with IBD in order to restore a healthy balance of gut bacteria. MBPs are living microorganisms that are designed to colonize the gut and restore a healthy microbiota [37].

Dr. Plevy's research has shown that both FMT and MBPs can be effective in reducing inflammation and improving symptoms in patients with IBD. He continues to work on developing new microbiome-based therapies and understanding the complex interactions between the gut microbiota and the immune system in IBD [38].

Dr. Plevy has also been studying microbial bio-therapeutic products (MBPs), which are living microorganisms that are designed to colonize the gut and restore a healthy microbiota. MBPs are specifically engineered to produce beneficial molecules or to inhibit harmful molecules, such as pro-inflammatory cytokines [39]. Dr. Plevy has been involved in clinical trials of several MBPs for IBD, including a phase 2 trial of a MBP that showed promising results in inducing remission in patients with ulcerative colitis.

In addition to developing new microbiome-based therapies, Dr. Plevy's research has also focused on understanding the complex interactions between the gut microbiota and the immune system in IBD [40]. He has identified specific microbial signatures that are associated with disease activity in patients with IBD, and has shown that these signatures can be used to predict response to therapy. Dr. Plevy's research has also highlighted the importance of the gut-brain axis in IBD, and the potential for neuromodulators to be used as therapeutic targets.

Studies on the Efficacy and Safety Preparations in the Treatment of IBD: Recent advances in the treatment of IBD have led to a paradigm shift in therapeutic goals away from the ideal of symptom-free everyday life and toward mucosal repair. To understand the benefits, harms, and research potential of different drugs and therapies and to provide a basis for clinical decision making and further research on IBD, this review reviews the latest advances in the treatment of IBD.

TABLE 3: SUMMARIZING VARIOUS STUDIES ON THE EFFICACY AND SAFETY OF DIFFERENT PREPARATIONS IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE (IBD)

Treatment	Efficacy Studies	Safety Studies	References
Aminosalicylates	- Sandborn et al. (2012): Efficacy of mesalamine in inducing remission in UC.	- Hawthorne et al. (2007): Safety profile of aminosalicylates in IBD patients.	Sandborn et al. (2012); Hawthorne et al. (2007) [41-42]
Corticosteroids	- Benchimol et al. (2008): Effectiveness of prednisone in CD treatment.	- Lewis et al. (2015): Adverse events associated with corticosteroid use in IBD.	Benchimol et al. (2008); Lewis et al. (2015) [43-44]
Immunomodulators	- Present et al. (1999): Efficacy of azathioprine in maintaining remission in CD.	- Lichtenstein et al. (2000): Safety profile of immunomodulators in IBD patients.	Present et al. (1999); Lichtenstein et al. (2000) [45-46]
Biologic Agents	- Sandborn et al. (2007): Efficacy of infliximab in moderate to severe UC.	- Lichtenstein et al. (2018): Safety outcomes of various biologic therapies.	Sandborn et al. (2007); Lichtenstein et al. (2018) [47-46]
Fecal Microbiota Transplantation (FMT)	- Paramsothy et al. (2017): Efficacy of FMT in UC patients.	- Moayyedi et al. (2019): Safety profile of FMT in IBD treatment.	Paramsothy et al. (2017); Moayyedi et al. (2019) [48-49]
JAK Inhibitors	- Panés et al. (2017): Efficacy of tofacitinib in UC treatment.	- Sandborn et al. (2019): Safety and tolerability of JAK inhibitors in IBD.	Panés et al. (2017); Sandborn et al. (2019) [50-51]

Drugs used in the Treatment of Inflammatory Bowel Disease (IBD): The term inflammatory bowel disease (IBD) refers to a group of chronic inflammatory diseases of the digestive system, including Crohn's disease and ulcerative colitis. The complex and multidimensional nature of these diseases has led to the development of a variety of therapeutic treatments over time. This collection lists the different classes of drugs used to treat IBD with the expected release dates of each supporting document. These interventions, ranging from traditional anti-inflammatory drugs to cutting-

edge biologics and cutting-edge treatments such as fecal microbiota transplantation, collectively illustrate advances in IBD treatment methods. Below a **Table 4** summarizing past to present drugs used in the treatment of Inflammatory Bowel Disease (IBD), along with their approximate introduction times, references, and brief explanations of their mechanisms of action

TABLE 4: SUMMARIZING PAST TO PRESENT DRUGS USED IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE (IBD)

Drug Category	Drugs	Introduction Times	Mechanism of Action	References
Aminosalicylates	Sulfasalazine, Mesalamine	1950s, 1980s	Modulate inflammatory pathways in the gut, acting on local inflammation.	Hanauer, S. B. (2006) [52]
Corticosteroids	Prednisone, Budesonide	1955, 1990s	Potent anti-inflammatory effect by suppressing immune responses.	D'Haens, G., &Vermeire, S. (2008) [53]
Immunomodulators	Azathioprine, Mercaptopurine, Methotrexate	1960s, 1960s, 1980s	Suppress the immune system to reduce inflammation and disease progression.	Sands, B. E. (1999) [54]
Biologic Agents	Infliximab, Adalimumab, Certolizumab, Vedolizumab, Ustekinumab	1998, 2002, 2008, 2014, 2016	Target specific molecules or pathways in the immune system to inhibit inflammation.	Danese, S., & Fiocchi, C. (2011) [55]
JAK Inhibitors	Tofacitinib	2012	Inhibit Janus kinase (JAK) signaling pathways, reducing inflammation.	Sandborn, W. J., Panés, J., & Sands, B. E. (2019) [56]
Fecal Microbiota Transplantation (FMT)	Introduced to clinical practice in recent years	-	Restore a balanced gut microbiota from a healthy donor, impacting immune responses.	Paramsothy, S., Kamm, M. A., & Kaakoush, N. O. (2017) [57]

TABLE 5: NEW DRUGS THAT ARE UNDER CLINICAL TRIALS FOR INFLAMMATORY BOWEL DISEASE (IBD)

Drug	Company	Clinical Trial Phase	Brief Description	References
Ozanimod	Celgene	Phase 3	Sphingosine 1-phosphate receptor modulator targeting lymphocyte trafficking.	Sandborn et al. (2016) [58]
Filgotinib	Gilead Sciences	Phase 2/3	Selective JAK1 inhibitor targeting inflammatory pathways.	Vermeire et al. (2019) [59]
Mirikizumab	Eli Lilly	Phase 2/3	Monoclonal antibody against IL-23, modulating inflammatory response.	Sandborn et al. (2021) [60]
RPC1063	Celgene	Phase 2	Selective sphingosine 1-phosphate receptor modulator with immunomodulatory effects.	Danese et al. (2020) [61]

DISCUSSION: Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract, which includes Crohn's disease and ulcerative colitis. The pathogenesis of IBD is complex and multifactorial, involving genetic, environmental, and immunological factors. The dysregulated immune response to commensal bacteria in the gut is a central feature of IBD pathogenesis [62]. Alterations in gut microbial ecology are a hallmark of IBD, and include decreased microbial diversity, an expansion of potentially harmful bacteria, and a loss of beneficial bacteria. These alterations are thought to contribute to the dysregulated immune response observed in IBD. The composition of the gut microbiota in IBD is distinct from that of healthy individuals, with an increase in Proteobacteria and a decrease in Firmicutes and Bacteroidetes. Cytokines play a crucial role in the pathogenesis of IBD. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (INF-γ), interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-12 (IL-12) are produced by immune cells in response to the presence of bacterial antigens in the gut [63]. These cytokines contribute to the chronic inflammation observed in IBD. In contrast, anti-inflammatory cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5), and

interleukin-10 (IL-10) have a protective effect in IBD by downregulating the immune response. Recent therapeutic strategies for IBD have focused on targeting the dysregulated immune response and restoring balance to the gut microbiota [64]. Microbiome-based therapies, such as fecal microbiota transplantation (FMT) and microbial biotherapeutic products (MBPs) have shown promise in clinical trials for inducing remission in patients with IBD. FMT is thought to work by restoring the balance of gut bacteria and reducing inflammation in the gut. MBPs are specifically engineered to produce beneficial molecules or to inhibit harmful molecules, such as pro-inflammatory cytokines. Other therapies, such as anti-TNF-α antibodies and anti-integrin antibodies, have been successful in reducing inflammation and improving symptoms in patients with IBD.

However, there are still gaps in our understanding of IBD pathogenesis and the efficacy and safety of current therapeutic strategies. For example, the mechanisms by which gut dysbiosis leads to a dysregulated immune response in IBD are not fully understood. Additionally, the long-term safety and efficacy of microbiome-based therapies are still being investigated. Further research is needed to identify novel therapeutic targets and develop personalized treatment strategies based on an individual's gut microbiota and immune profile.

CONCLUSION: Inflammatory bowel disease (IBD) is a complex disease with a multifactorial etiology that involves genetic, environmental, and immunological factors. The current understanding of the pathogenesis of IBD suggests that a dysregulated immune response to commensal bacteria in the gut plays a central role in the development and progression of the disease. Alterations in gut microbial ecology are a hallmark of IBD, and include decreased microbial diversity, an expansion of potentially harmful bacteria, and a loss of beneficial bacteria. These alterations in the gut microbiota are thought to contribute to the dysregulated immune response observed in IBD. Cytokines play a crucial role in the pathogenesis of IBD, particularly pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-12 (IL-12). These cytokines are produced by immune cells in response to the presence of bacterial antigens in the gut, and contribute to the chronic inflammation observed in IBD. Recent therapeutic strategies for IBD have focused on targeting the dysregulated immune response and restoring balance to the gut microbiota. Microbiome-based therapies, such as faecal microbiota transplantation (FMT) and microbial bio-therapeutic products (MBPs), have shown promise in clinical trials for inducing remission in patients with IBD. Other therapies, such as anti-TNF-α antibodies and anti-integrin antibodies, have been successful in reducing inflammation and improving symptoms in patients with IBD.

However, there are still gaps in the literature and areas for future research. For example, the mechanisms by which gut dysbiosis leads to a dysregulated immune response in IBD are not fully understood. Additionally, the long-term safety and efficacy of microbiome-based therapies are still being investigated. Future research should also focus on identifying novel therapeutic targets for IBD, as well as developing personalized treatment strategies based on an individual's gut microbiota and immune profile.

One area that has received less attention in IBD research is the role of the gut microbiome and its interaction with the immune system. The gut microbiome is a complex ecosystem of microorganisms that play a vital role in maintaining gut health and modulating the immune system. While there is evidence to suggest that alterations in the gut microbiome composition and function can contribute to the development and progression of IBD, more research is needed to fully understand the mechanisms underlying these interactions. Additionally, there is a need for further research into the development of novel therapies for IBD. While current therapies can be effective in managing symptoms and reducing inflammation, they are not curative and can have significant side effects. Developing new therapies that target specific pathways involved in the pathogenesis of IBD could improve treatment outcomes and quality of life for people with IBD. Overall, while significant progress has been made in IBD research, there is still much to be done to fully understand the complex pathophysiology of this condition and develop more effective treatments.

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