IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

REVIEW OF NOVEL PHARMACOLOGICAL INSIGHTS INTO INTESTINAL HEALING AND INFLAMMATORY DISORDERS

[1] Mr.Shivam Tate, [2] Hrukshikesh Warade [3] Dr. V.Y.Lokhande

[1]student M.Pharm [2]student M.Pharm, [3]principal

Pharmacology,

Arvind Gavali College Jaitapur Satara

Abstract: Chronic inflammation is a common trait in the pathogenesis of several dis- eases of the gut, including inflammatory bowel disease and celiac disease. Control of the inflammatory response is crucial in these pathologies to avoid tissue destruction and loss of intestinal function. Over the last 50 years, the identification of the mechanisms and mediators involved in the acute phase of the inflammatory response, which is characterized by massive leukocyte recruitment, has led to a number of therapeutic options. New drugs targeting inflammatory flares are still under development. However, interest on the other end of the spectrum—the resolution and repair phases—has emerged, as promoting tissue functional repair may maintain remission and counter- act the chronicity of the disease. This review aims to discuss the current and future pharmacological approaches to the treatment of chronic intestinal inflammation and the restoration of functional tissues.

Introduction

this study secondary data has been collected. From the website of KSE the monthly stock prices for the sample firms are obtained from Jan 2010 to Dec 2014. And from the website of SBP the data for the macroeconomic variables are collected for the period of five years. The time series monthly data is collected on stock prices for sample firmsand relative macroeconomic variables for the period of 5 years. The data collection period is ranging from January 2010 to Dec 2014. Monthly prices of KSE -100 Index is taken from yahoo finance.

INFLAMMATION: WHY? WHEN? HOW?

Inflammation is the body’s response to harmful stimuli such as pathogens, toxic compounds, or damaged cells. It acts to remove the injurious stimuli and to initiate repair and functional healing processes. It is characterized by different phases (Figure 1): a silent phase, where a number of mediators are released by damaged or aggressed cells to initiate the inflammatory response; a vascular phase, which is associated with vasodilation and plasma extravasation; a cellular phase, characterized by the infiltration of inflammatory cells such as neutrophils, monocytes,and macrophages, which can be followed by the activation of the adaptative immunity; and finally a resolution phase, which repairs tissues and clears the debris and the infiltrated inflammatory cells. Therefore, by definition inflammation is a physiological process with a beginning, a middle, and an end.

However, some patients can develop chronic inflammatory disorders, defined by inflammatory symptoms that persist for several months to years. Chronic inflammation can result from the fail- ure to eliminate the agent causing the acute inflammatory response.

That can happen in cases of infection by pathogens (e.g., bacteria, fungi, parasites) that resist or counteract host defense mechanisms, as well as in cases where exposure to the irritant is constant and the irritant can- not be degraded by endogenous mechanisms (e.g., enzymes, engulfment by inflammatory cells)(3). Chronic inflammation also occurs in autoimmune disorders, where the immune system rec- ognizes self-proteins as foreign antigens and organizes tissue destruction, as in celiac disease (4).

Dysregulation of the resolution mechanisms, which normally represent the end of the inflamma- tory process, could also be responsible for chronic inflammation (5). At mucosal surfaces such as the intestine, malfunction of the mechanisms involved in "handling" foreign antigens and microor- ganism exposure by mucosal tissues could also explain chronic inflammatory disorders. Among these malfunctioning mechanisms is the barrier function, in all its dimensions—physical (mucus), cellular (epithelial cells), and immunological (resident inflammatory cells) (6).

DISEASES ASSOCIATED WITH INTESTINAL INFLAMMATION

Episodes of acute ileitis or colitis are usually associated with infectious events (viral, bacterial, fungal, or parasitic). If a specific pathogen is identified as the cause of this acute inflammation, an- tibiotics or antiparasitic treatments can be prescribed, but in most cases, the inflammatory event resolves by itself. However, in some cases, acute ileitis or colitis may represent the first mani- festation of chronic inflammatory disorders, which have to be carefully defined and diagnosed and which frequently require pharmacological interventions (7). These chronic inflammatory disorders of the gut include IBD, celiac disease, and irritable bowel syndrome (IBS).

Inflammatory Bowel Disease

IBD is a chronic inflammatory disorder of the gut. It includes two major subtypes, Crohn's dis- ease (CD) and ulcerative colitis (UC), which are associated with general abdominal pain, diarrhea, and bloody stools. IBD consists of episodes of acute inflammation (flares) followed by remission periods and relapses (Figure 1). In terms of etiology, the consensus is that IBD develops in in- dividuals who are both genetically susceptible and exposed to a propitious environment, which together lead to modification of intestinal microbiota and an uncontrolled immune response.

Celiac Disease

Celiac disease is a hereditary immunological disorder. In genetically susceptible individuals, mucosal inflammation and villous atrophy develop in the small intestine following the dietary ingestion of gluten. The high glutamine and proline content in wheat gliadins and glutenins ren- ders these proteins resistant to proteolytic degradation, leading to the presence of immunogenic large peptides in the small intestine. However, the presence of these peptides is not sufficient to develop the disease; patients must also have specific HLA class II genes that map the DQ locus. This genetic predisposition renders intestinal tissues more prone to a food-based inflammatory trigger (4).

Given the central role of gluten in the pathogenesis of celiac disease, a strict gluten-free diet is the recommended treatment.The Particular Case of Irritable Bowel SyndromeIBS is a painful chronic abdominal syndrome associated with altered bowel habits, for which the underlying structural abnormalities or inflammatory cell infiltration has not been identified. Many studies have investigated whether signs of inflammation are associated with this syndrome (8). Some studies have demonstrated that anti-inflammatory treatments (e.g., mesalazine) did not al- leviate IBS symptoms, thereby suggesting that inflammation is not responsible for IBS symptoms (9–11). However, strong evidence for increased activation of immune cells has been found in a large proportion of IBS patients (12). These immune cells include mast cells, which were de- granulated in colon tissues from IBS patients (13, 14), and various proinflammatory mediators (histamine, polyunsaturated fatty acid metabolites, proteases), which were upregulated in colonic biopsies of IBS patients (12–16). Therefore, sufficient evidence suggests that IBS can be consid- ered a low-grade, chronic, inflammatory disorder of the gut, in which inflammatory cell infiltration is clearly not an associated feature, but where tissue dysfunction and altered mucosal homeostasis may occur.

MOLECULAR MECHANISMS INVOLVED IN INTESTINAL INFLAMMATION

Common features of an inflammatory state of intestinal mucosa include microbiota biofilm dys- biosis, epithelial dysfunction, innate immune cell infiltration, and activation of adaptive immunity (Figure 2). Microbiota dysbiosis might not present the exact same taxonomic profiles in IBD, celiac disease, or IBS; therefore, common microbial molecular mechanisms are difficult to iden- tify. However, a decrease in the diversity and richness of microbial species is common in all of these inflammatory states (17–19). Altered barrier function is another common trait (20). Degradation of intestinal epithelial cells' tight-junction molecules, such as zonulin and occludin, is associated with gut inflammation, as is reduced production of mucus by goblet cells (21).

The expression and se- cretion of antimicrobial peptides by Paneth cells and enterocytes are also major components of the intestinal barrier function, which decreases upon inflammation (22). α- and β-defensins, lysozyme, and protease inhibitors such as elafin and secretory leukocyte protease inhibitor, which act as an- timicrobial peptides, are downregulated in inflamed tissues (22–25). Promoting the expression and function of tight-junction molecules, mucous proteins, and antimicrobial peptides would there- fore help reinforce the intestinal barrier function and is considered a therapeutic approach to the treatment of inflammation.

Microbiota dysbiosis and altered barrier function set the stage for an increased and abnor- mal tissue exposure to microorganisms, resulting in a profound activation of innate immune cells. Activated macrophages engulf microbial motives and release tumor necrosis factor α (TNF-α), interleukin (IL)-6, IL-12, and IL-23 (Figure 2), through signaling mechanisms that involve Toll- like receptor 9, phosphodiesterase 4, and Janus kinase (JAK). All of these mediators and signaling pathways are considered important molecular targets for the treatment of chronic inflammation(25).

Upon their activation by tissue damage or invasion, mast cells, macrophages, and neutrophils collectively release molecules stored in their granules. Among these molecules are lipidic media- tors of inflammation, including prostaglandins and leukotrienes, as well as reactive oxygen species (ROS) and proteases, all of which constitute molecular targets for the treatment of inflammation (Figure 2) (26). Intestinal epithelial cells also contribute to the release of these.

mediators in the inflamed gut mucosa.In chronic inflammatory disorders, the adaptive immune system kicks in with dendritic cells, which migrate to mesenteric lymph nodes to present antigens to naive T cells. This process leads to the proliferation and differentiation of effector T helper 1 and 17 (Th1 and Th17) cells under

PHARMACOLOGICAL APPROACHES TARGETING CHRONIC GUT INFLAMMATION

The vast majority of the drugs that are currently used to treat chronic intestinal inflammation either target inflammatory mediators released in the early phases of the inflammatory response (i.e., the silent and vascular phases) or target the recruitment of inflammatory cells.

Aminosalicylates

Aminosalicylates, including sulfasalazine and 5-ASA, target the metabolism of arachidonic acid, inhibiting the release of lipidic mediators of inflammation from the prostaglandin and leukotriene families. However, this class of drugs is suspected to harbor additional mechanisms of action, in- cluding scavenging ROS, inhibiting cytokine production by leukocytes, inducing regulatory T cell recruitment through an aryl hydrocarbon receptor–dependent pathway, and binding to peroxi- some proliferator-activated receptor γ (28–30). 5-ASA is used to treat UC, where it helps maintain remission, but its use in CD patients remains controversial.

While one study reported that 5-ASA is effective at decreasing oxidative burst and inflamma- tion in organotypic cultures of tissues of celiac disease patients, its use has not been reported to reduce tissue inflammation (31). Studies in IBS patients reported that 5-ASA treatment did not modify symptoms (9, 11).

Corticosteroids

In the 1950s, corticosteroids became the first pharmacological approach to the treatment of IBD, and their use still leads to effective remission in many patients. They have not proved effective in maintaining remission. As a result, corticosteroids are used to stop inflammatory flares and induce remission but are not considered for long-term use.

The pleiotropic effects of corticosteroids on all the pathways involved in inflammation explain their efficacy. However, despite efforts to develop corticosteroids with better safety and tolerability, their use can have significant side effects, including opportunistic infections, diabetes mellitus, hypertension, venous thromboembolism, and osteoporosis. In addition, some patients are resistant to corticosteroid treatments and must be considered for other immunomodulatory approaches.

Immunomodulators

Immunomodulators used for the treatment of gut inflammation include thiopurines, methotrex- ate, calcineurin inhibitors, and JAK inhibitors, all of which aim to reduce T lymphocyte activation or proliferation and are very effective at reducing inflammatory flares. However, they also cause many adverse effects, including liver injury, bone marrow suppression, and infectious diseases.

Biologics

Many of the biologics used in the treatment of intestinal inflammation, particularly IBD, target cytokines or integrins. Because TNF-α, IL-12, and IL-23 play a major role in the pathogenesis of IBD, anti-TNF-α and anti-IL-12/23 antibodies are the major biologics that are used for the treatment of IBD.

Anti-TNF-α antibodies can inhibit both the inflammatory response and tissue damage. They are prescribed to patients with moderate to severe UC or CD who do not respond to corticosteroids. Long-term remission with anti-TNF-α antibodies can be achieved through dose escalation.

However, up to 40% of patients do not respond to TNF-α inhibitors, and between 20% and 45% of patients experience secondary loss of response only 1 year after the start of anti- TNF-α treatment (32). As a result, anti-IL-12 and anti-IL-23 are often used in these patients as a second-line therapy, since they are effective in both biologic-naive and -experienced patients (33).

Integrins are at the forefront of inflammatory cell recruitment and retention in inflamed tissues because they mediate the homing of leukocytes through binding to tissue-specific cell adhesion molecules. Anti-integrin therapy blocks the binding of integrin at the leukocyte surface to en- dothelial cell adhesion molecules or to E-cadherin expressed on epithelial cells.

Anti-integrin biologics target either the γ4 or the β7 integrin subunit of the adhesion molecules.All biologics are very effective at inducing remission in responders. However, despite their advantages of high selectivity and specificity, primary no response, secondary loss of response, and therapeutic intolerance are still high in a proportion of IBD patients, so other therapeutic options are necessary.Targeting the MicrobiotaMicrobiota dysbiosis is not only a common feature of intestinal pathologies associated with in- flammation but also an early event contributing to long-term inflammation.

Therefore, targeting the microbiota appears to be an interesting therapeutic option for the treatment of intestinal inflammation (34). From a pharmacological perspective, however, such approaches have been challenging.

First, the complexity of the microbiome (which consists of trillions of microor- ganisms interacting with one another) and the difficulty of fully reproducing this complexity in culture models have made microbiome-targeted approaches empirical. Second, microbiome-based therapies range from dietary interventions, prebiotic supplementation, single- or multiprobiotic strain administration, and phage therapy to human donor–derived fecal microbiota transplantation (FMT) and microbiome mimetics.

Quality control, precise dosing of live biotherapeutics, treat- ment frequency, delivery mode, and determination of bioavailability are data that are extremely challenging to collect (35). Nonetheless, several lines of evidence suggest that microbiome- targeted therapies may have some benefits for IBD (18, 36), IBS (17), and to a certain extent celiac disease (37).

The mode of action of microbiome-based therapies is probably multimodal, involving direct effects on biofilm composition and metabolism, control of barrier function, and influence on mucosal immunity (34). However, considerable research is still needed to understand the mechanisms of action and to optimize and define reliable conditions for microbiome-based therapeutic prescription in the clinic.

PROMOTING REPAIR: WHAT PHARMACOLOGY?

All of the current therapeutic approaches to the treatment of intestinal inflammation focus either on inhibiting early mediators of the silent/vascular phases or on inhibiting the cellular phase of leukocyte recruitment. In this sense, they all aim to induce remission but do not necessarily succeed at maintaining it. Therefore, the goals of clinical studies are not only to stop flares by inducing remission but also to achieve complete histological repair of the damaged tissues (38).

Mucosal healing has become a key endpoint in clinical trials (39). To lead the way, better knowledge of the mechanisms involved in tissue repair is crucial. To achieve long-term and successful remission, the tissues must return to functionality and homeostasis. Different mediators and actors of resolution and repair are currently under investigation to serve as potential targets for drug development focusing on functional repair of intestinal mucosa (Figure 3).Following a bout of inflammation, repair is triggered by the inflammatory mechanisms themselves.

This first step, described as resolution of inflammation, starts with the initiation of neutrophil apoptosis, which promotes efferocytosis, and the recruitment of monocytes and macrophages (under the control of 15-lipoxygenase), which induce a proresolving response char- acterized by M2 macrophage differentiation and the recruitment of suppressive regulatory T cells(40). All of these events are controlled by specialized proresolving mediators including lipoxins, resolvins, protectins, and maresins.

The role and importance of these resolution mechanisms in chronic inflammatory disorders of the gut have been studied mostly in animal models, although proresolving mediators have been identified in human tissues in IBD (41). Engineered regula- tory T cells have been tested in IBD patients but have demonstrated limited efficacy (42). Further clinical studies are needed to determine the pharmacology and potential effects of proresolving mediators in human intestinal inflammation.

Mucosal healing relies on the coordinated activity of intestinal epithelial cells to replace dam- aged epithelium and to restore full barrier and secretory function. Intestinal epithelial cells at the edges of epithelial wounds lose their columnar polarity and migrate to initiate a process called epithelial restitution (43) .
This process is regulated by cytokines such as transforming growth factor beta (TGF-β), epidermal growth factor, IL-1β, and interferon-γ (44), as well as by molecules secreted by the epithelium itself such as trefoil peptides, galectins, and proteases or their inhibitors (45–47). As soon as the acute inflammatory flare is attenuated, intestinal epithelial cells proliferate, expand, migrate, and differentiate to close the epithelial wounds caused by the inflam- matory response. These mechanisms are controlled by many molecules of host origin, including the regenerating protein family, defensins, antimicrobial peptides, proteases, and mucins, but they also are modulated by microbiota.

A challenge in developing new pharmacological approaches to encourage mucosal repair is to determine the most prominent pathway to target. The recovery of intestinal barrier function and of the secretory mechanisms involved in handling mucosal microbiota has attracted attention, and new therapeutic options that target microbiota ecology, stem cell function, and barrier function are currently under investigation in both preclinical and clinical studies.

Microbiota-Associated Repair

Changes in the composition and metabolic activity of the intestinal microbiota occur in patients with chronic inflammatory disorders of the gut, namely IBD (CD and UC), celiac disease, and IBS. These changes can trigger an abnormal immune response in genetically predisposed patients with IBD (48) and celiac disease, and they can lead to constant, low-grade inflammation in patients with IBS (17). Several ways to improve the intestinal microecology in these patients have been proposed.

Initial clinical studies in both CD and UC patients demonstrated the positive effects of an- tibiotics (49). However, more recent reviews reported that antibiotics are only modestly effective at inducing remission and that the effects of antibiotics at maintaining remission status in CD and UC patients are unclear (50, 51). Long-term exposure to antibiotics, particularly with broad- spectrum coverage and in children, appears to be detrimental, with a higher risk of new onset of IBD (52).

Therefore, the use of antibiotics as a future treatment for IBD has not been established. Multiple studies have demonstrated the potential effects of pre-, pro-, and postbiotics in IBD and IBS patients. They all appear to be safe and well tolerated, although their effects are sometimes quite limited (53).

In patients with CD, most studies have shown that probiotics have no significant effects, while in patients with UC (54) or IBS (17), they have beneficial effects on clinical symptoms and remission.

Finally, the potential of FMT in the treatment of IBD is actively being investigated. FMT performs better than placebo at achieving clinical remission in UC patients (55), and a meta-analysis of the efficacy of FMT in patients with IBD reported that the clinical remission rate is significant in both CD and UC (56). Clinical studies are ongoing, and while findings on the induction of remission are beginning to be reported, we are still waiting for clear results regarding the maintenance of remission. However, the lack of unified standards for the use of FMT, such as for donor selection, route of administration, and whether or not to pretreat with antibiotics, limits the use of FMT in clinical practice.

Stem Cell Transplantation

Since stem cells are possibly the origin of all cell types, including epithelial cells, it is logical to consider stem cell therapy for the repair of injured intestinal tissues and the restoration of their function. Beneficial effects in severe refractory CD patients have been reported following autol- ogous treatment with hematopoietic stem cells (57) or administration of allogeneic bone marrow mesenchymal stem cells (half of the patients achieved clinical remission) (58). Interestingly, while most of the CD patients in a cohort study relapsed after 5 years following transplantation of au- tologous hematopoietic stem cells, 80% of the relapsed patients returned to clinical remission after a new treatment with hematopoietic stem cells (59).

Positive results on healing of complex anal fistula were also reported in CD patients who received allogeneic adipose tissue–derived stem cell therapy (60, 61). Thus, stem cell transplantation has a potential therapeutic effect on mucosa repair in patients with CD. However, the clinical use of stem cell transplantation has yet to be ap- proved. Possible adverse effects have to be carefully documented, and the conditions of stem cell production and use (e.g., number of cells, quality control) have to be standardized. Finally, stem cell transplantation could also employ autologous intestinal stem cells, which would be cultured and tested in vitro prior to transplantation. This approach has already been used successfully in animal models (62), but its conditions of use in humans have yet to be established.

Strengthening Barrier Function

Defective barrier function is associated with intestinal inflammation and has been observed in pa- tients with IBD, celiac disease, and IBS. Many studies have reported that barrier function remains altered for several weeks after a bout of inflammation, even in the absence of signs of inflamma- tion. Restoration of barrier function once the acute inflammatory response has been cleared is a major step in tissue repair processes.

Several factors are involved in barrier function: (a) microbial biofilms at the mucosal surface, (b) the mucous layer, (c) the epithelial monolayer, (d) the underly- ing mucosal immune system, and (e) mucosal innervation (63). Therefore, barrier function may be restored through various approaches. Some IBD treatments act, at least in part, on the restoration of epithelial barrier function, and anti-TNF-α therapy is effective in patients with CD (64Clinically, the focus of therapies targeting intestinal barrier function has been on dietary ap- proaches, namely immunomodulatory nutrients, probiotics, and microbial metabolites. Topical butyrate is efficacious in strengthening barrier function in patients with refractory UC (65).

Fatty acids such as omega-3 and phosphatidylcholine have been proposed as adjuvant therapies to strengthen barrier function and maintain remission in IBD patients (66, 67). Oral zinc therapy restores intestinal barrier function in CD patients by a mechanism involving tight-junction modu- lation (68, 69). Polymorphism of the vitamin D receptor has been associated with the development of IBD (70), and vitamin D is known to be involved in maintaining barrier function (71).

Thus, it is logical to consider the use of vitamin D to help reduce the increased intestinal permeability associated with intestinal inflammation in IBD, celiac disease, and IBS. Whether it would affect the maintenance of remission is not known.

Other mechanisms involved in epithelial permeability, such as myosin light-chain kinases, have been the subject of preclinical studies. However, much of this research was performed in animal models, and no therapeutic approaches based on these mechanisms have been proposed for clinical studies in humans.

FUTURE CONCEPTS

In the new conception of chronic inflammatory disorders described in the literature reviewed here, patients whose genetic background leads to malfunctioning cells can be predisposed to au- toimmune responses. The fragility of these cells due to genetic predisposition may render them more prone to inflammatory triggers.

In the gut, lumenal content is probably the primary inflam- matory trigger, but it can hardly be dampened. Therefore, targeting the specific genetic disorder and attempting to alleviate tissue-resident cellular dysfunction and fragility represent an avenue for therapeutic intervention.

Genome-wide association studies in IBD have identified more than 200 loci as contributing risk factors to the disease (72, 73). Furthermore, targeted approaches have revealed disease-associated coding variants, which have been studied functionally to demon- strate their causal relationship with the disease (74, 75). However, most of these functional studies were performed in genetically transformed mice, and questions persist as to the contribution of these variants in the course of human disease

In the future, specific gene therapy approaches in genotyped patients might be considered in combination with, or as a follow-up treatment to, classical anti-inflammatory therapies. Such approaches might stabilize the disease for an extended period of time or even be curative. However, at present, harnessing the vast array of genetic dis- coveries in IBD for clinical application remains extremely challenging.

Genotyping studies have focused on loci with common variants that might not always match the causative variants. Many of the variants identified are in noncoding regions, and we do not yet understand how they might alter gene expression. In the near future, such genetic data will likely be used in the clinic as biomarkers or for drug development in a very small population of patients, such as very early onset cases.Genetic studies might also be applied to determine different outcomes to treatments. Such studies could be especially fruitful for biologics, since studies have reported significant associations between polymorphism identification and treatment response (76, 77). In the future, pretherapy genotyping could be employed to predict the best response to treatments with biologics.

CONCLUSIONS

A wide array of therapeutic options are available to treat chronic inflammatory disorders of the gut, particularly IBD. The most developed therapies involve targeting the acute phase of the inflam- matory response with the goal of reducing inflammatory cell infiltrates, and additional treatments in this field are expected.

LITERATURE CITED

1. Imbrizi M, Magro F, Coy CSR. 2023. Pharmacological therapy in inflammatory bowel diseases: a narrative review of the past 90 years. Pharmaceuticals 16:1272
2. Nathan C, Ding A. 2010. Nonresolving inflammation. Cell 140:871–82
3. Cavaillon JM. 2021. Once upon a time, inflammation. J. Venom. Anim. Toxins Incl. Trop. Dis. 27:e20200147
4. Barone MV, Auricchio R, Nanayakkara M, Greco L, Troncone R, Auricchio S. 2022. Pivotal role of inflammation in celiac disease. Int. J. Mol. Sci. 23:7177
5. Buckley CD, Gilroy DW, Serhan CN, Stockinger B, Tak PP. 2013. The resolution of inflammation. Nat. Rev. Immunol. 13:59–66
6. Michielan A, D'Inca R. 2015. Intestinal permeability in inflammatory bowel disease: pathogenesis, clinical evaluation, and therapy of leaky gut. Mediat. Inflamm. 2015:628157
7. Levartovsky A, Ovdat T, Barash Y, Ben-Shatach Z, Skinezes Y, et al. 2022. Signs and symptoms of acute bowel inflammation and the risk of progression to inflammatory bowel disease: a retrospective analysis.
8. J. Clin. Med. 11:4595
9. Collins SM, Piche T, Rampal P. 2001. The putative role of inflammation in the irritable bowel syndrome.
10. Gut 49:743–45
11. Barbara G, Cremon C, Annese V, Basilisco G, Bazzoli F, et al. 2016. Randomised controlled trial of mesalazine in IBS. Gut 65:82–90
12. Lam C, Tan W, Leighton M, Hastings M, Lingaya M, et al. 2016. A mechanistic multicentre, parallel group, randomised placebo-controlled trial of mesalazine for the treatment of IBS with diarrhoea (IBS-D). Gut 65:91–99
13. Andrews CN, Griffiths TA, Kaufman J, Vergnolle N, Surette MG, Rioux KP. 2011. Mesalazine (5-aminosalicylic acid) alters faecal bacterial profiles, but not mucosal proteolytic activity in diarrhoea-predominant irritable bowel syndrome. Aliment. Pharmacol. Ther. 34:374–83
14. Barbara G, Cremon C, Carini G, Bellacosa L, Zecchi L, et al. 2011. The immune system in irritable bowel syndrome. J. Neurogastroenterol. Motil. 17:349–59
15. Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, et al. 2004. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology 126:693–702
16. Cenac N, Andrews CN, Holzhausen M, Chapman K, Cottrell G, et al. 2007. Role for protease activity in visceral pain in irritable bowel syndrome. J. Clin. Investig. 117:636–47
17. Rolland-Fourcade C, Denadai-Souza A, Cirillo C, Lopez C, Jaramillo JO, et al. 2017. Epithelial expression and function of trypsin-3 in irritable bowel syndrome. Gut 66:1767–78
18. Cenac N, Bautzova T, Le Faouder P, Veldhuis NA, Poole DP, et al. 2015. Quantification and potential functions of endogenous agonists of transient receptor potential channels in patients with irritable bowel syndrome. Gastroenterology 149:433–44.e7
19. Marasco G, Cremon C, Barbaro MR, Stanghellini V, Barbara G. 2022. Gut microbiota signatures and modulation in irritable bowel syndrome. Microbiome Res. Rep. 1:11
20. Oka A, Sartor RB. 2020. Microbial-based and microbial-targeted therapies for inflammatory bowel diseases. Dig. Dis. Sci. 65:757–88
21. Galipeau HJ, Verdu EF. 2022. The double-edged sword of gut bacteria in celiac disease and implications for therapeutic potential. Mucosal Immunol. 15:235–43
22. Barbara G, Barbaro MR, Fuschi D, Palombo M, Falangone F, et al. 2021. Inflammatory and microbiota- related regulation of the intestinal epithelial barrier. Front. Nutr. 8:718356
23. Okumura R, Takeda K. 2018. Maintenance of intestinal homeostasis by mucosal barriers. Inflamm. Regen.
24. 38:5
25. Ra YE, Bang YJ. 2024. Balancing act of the intestinal antimicrobial proteins on gut microbiota and health.
26. J. Microbiol. 62:167–79
27. Filipp D, Brabec T, Voboril M, Dobes J. 2019. Enteric α-defensins on the verge of intestinal immune tolerance and inflammation. Semin. Cell Dev. Biol. 88:138–46

28. Motta JP, Bermudez-Humaran LG, Deraison C, Martin L, Rolland C, et al. 2012. Food-grade bacteria expressing elafin protect against inflammation and restore colon homeostasis. Sci. Transl. Med. 4:158ra44
29. Deraison C, Bonnart C, Langella P, Roget K, Vergnolle N. 2023. Elafin and its precursor trappin-2: What is their therapeutic potential for intestinal diseases? Br. J. Pharmacol. 180:144–60
30. Saez A, Herrero-Fernandez B, Gomez-Bris R, Sánchez-Martinez H, Gonzalez-Granado JM. 2023. Pathophysiology of inflammatory bowel disease: innate immune system. Int. J. Mol. Sci. 24:1526
31. Chang JT. 2020. Pathophysiology of inflammatory bowel diseases. N. Engl. J. Med. 383:2652–64 Punchard NA, Greenfield SM, Thompson RP. 1992. Mechanism of action of 5-arninosalicylic acid.
32. Mediat. Inflamm. 1:151–65
33. Oh-Oka K, Kojima Y, Uchida K, Yoda K, Ishimaru K, et al. 2017. Induction of colonic regulatory T cells by mesalamine by activating the aryl hydrocarbon receptor. Cell Mol. Gastroenterol. Hepatol. 4:135–51
34. Rousseaux C, Lefebvre B, Dubuquoy L, Lefebvre P, Romano O, et al. 2005. Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor γ. J. Exp. Med. 201:1205–15
35. Benedetti E, Viscido A, Castelli V, Maggiani C, d'Angelo M, et al. 2018. Mesalazine treatment in organotypic culture of celiac patients: comparative study with gluten free diet. J. Cell. Physiol. 233:4383–90
36. Ben-Horin S, Kopylov U, Chowers Y. 2014. Optimizing anti-TNF treatments in inflammatory bowel disease. Autoimmun. Rev. 13:24–30
37. Wong U, Cross RK. 2019. Expert opinion on interleukin-12/23 and interleukin-23 antagonists as potential therapeutic options for the treatment of inflammatory bowel disease. Expert Opin. Investig. Drugs 28:473–79
38. Bethlehem L, Estevinho MM, Grinspan A, Magro F, Faith JJ, Colombel JF. 2024. Microbiota therapeutics for inflammatory bowel disease: the way forward. Lancet Gastroenterol. Hepatol. 9:476–86
39. Gulliver EL, Young RB, Chonwerawong M, D'Adamo GL, Thomason T, et al. 2022. The future of microbiome-based therapeutics. Aliment. Pharmacol. Ther. 56:192–208
40. Hu KA, Gubatan J. 2023. Gut microbiome–based therapeutics in inflammatory bowel disease. Clin. Transl. Discov. 3:e182
41. Saviano A, Petruzziello C, Brigida M, Morabito Loprete MR, Savioli G, et al. 2023. Gut microbiota alteration and its modulation with probiotics in celiac disease. Biomedicines 11:2638
42. Battat R, Duijvestein M, Guizzetti L, Choudhary D, Boland BS, et al. 2019. Histologic healing rates of medical therapies for ulcerative colitis: a systematic review and meta-analysis of randomized controlled trials. Am. J. Gastroenterol. 114:733–45
43. Pineton de Chambrun G, Peyrin-Biroulet L, Lemann M, Colombel JF. 2010. Clinical implications of mucosal healing for the management of IBD. Nat. Rev. Gastroenterol. Hepatol. 7:15–29
44. Onali S, Favale A, Fantini MC. 2019. The resolution of intestinal inflammation: the peace-keeper's perspective. Cells 8:344
45. Gobbetti T, Dalli J, Colas RA, Federici Canova D, Aursnes M, et al. 2017. Protectin D1n-3 DPA and resolvin D5n-3 DPA are effectors of intestinal protection. PNAS 114:3963–68
46. Desreumaux P, Foussat A, Allez M, Beaugerie L, Hebuterne X, et al. 2012. Safety and efficacy of antigen- specific regulatory T-cell therapy for patients with refractory Crohn's disease. Gastroenterology 143:1207– 17.e2
47. Sturm A, Dignass AU. 2008. Epithelial restitution and wound healing in inflammatory bowel disease.
48. World J. Gastroenterol. 14:348–53
49. Dignass AU, Podolsky DK. 1993. Cytokine modulation of intestinal epithelial cell restitution: central role of transforming growth factor β. Gastroenterology 105:1323–32
50. Paclik D, Lohse K, Wiedenmann B, Dignass AU, Sturm A. 2008. Galectin-2 and -4, but not galectin-1, promote intestinal epithelial wound healing in vitro through a TGF-β-independent mechanism. Inflamm. Bowel Dis. 14:1366–72
51. Dignass A, Lynch-Devaney K, Kindon H, Thim L, Podolsky DK. 1994. Trefoil peptides promote epithelial migration through a transforming growth factor β–independent pathway. J. Clin. Investig. 94:376– 83

52. Motta J-P, Magne L, Descamps D, Rolland C, Squarzoni-Dale C, et al. 2011. Modifying the protease, antiprotease pattern by elafin overexpression protects mice from colitis. Gastroenterology 140:1272–82
53. Ott SJ, Musfeldt M, Wenderoth DF, Hampe J, Brant O, et al. 2004. Reduction in diversity of the colonic mucosa associated bacterial microflora in patients with active inflammatory bowel disease. Gut 53:685–93
54. Khan KJ, Ullman TA, Ford AC, Abreu MT, Abadir A, et al. 2011. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. Am. J. Gastroenterol. 106:661–73
55. Townsend CM, Parker CE, MacDonald JK, Nguyen TM, Jairath V, et al. 2019. Antibiotics for induction and maintenance of remission in Crohn's disease. Cochrane Database Syst. Rev. 2:CD012730
56. Harbord M, Eliakim R, Bettenworth D, Karmiris K, Katsanos K, et al. 2017. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: Current management. J. Crohn's Colitis 11:769–84
57. Shaw SY, Blanchard JF, Bernstein CN. 2010. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. Am. J. Gastroenterol. 105:2687–92
58. Ganji-Arjenaki M, Rafieian-Kopaei M. 2018. Probiotics are a good choice in remission of inflammatory bowel diseases: a meta analysis and systematic review. J. Cell. Physiol. 233:2091–103
59. Kaur L, Gordon M, Baines PA, Iheozor-Ejiofor Z, Sinopoulou V, Akobeng AK. 2020. Probiotics for induction of remission in ulcerative colitis. Cochrane Database Syst. Rev. 3:CD005573
60. Moayyedi P, Surette MG, Kim PT, Libertucci J, Wolfe M, et al. 2015. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. Gastroenterology 149:102–9.e6
61. Paramsothy S, Paramsothy R, Rubin DT, Kamm MA, Kaakoush NO, et al. 2017. Faecal microbiota transplantation for inflammatory bowel disease: a systematic review and meta-analysis. J. Crohn's Colitis 11:1180–99
62. Duijvestein M, Vos AC, Roelofs H, Wildenberg ME, Wendrich BB, et al. 2010. Autologous bone marrow– derived mesenchymal stromal cell treatment for refractory luminal Crohn's disease: results of a phase I study. Gut 59:1662–69
63. Forbes GM, Sturm MJ, Leong RW, Sparrow MP, Segarajasingam D, et al. 2014. A phase 2 study of allogeneic mesenchymal stromal cells for luminal Crohn's disease refractory to biologic therapy. Clin. Gastroenterol. Hepatol. 12:64–71
64. Lopez-Garcia A, Rovira M, Jauregui-Amezaga A, Marin P, Barastegui R, et al. 2017. Autologous haematopoietic stem cell transplantation for refractory Crohn's disease: efficacy in a single-centre cohort.
65. J. Crohn's Colitis 11:1161–68
66. Dietz AB, Dozois EJ, Fletcher JG, Butler GW, Radel D, et al. 2017. Autologous mesenchymal stem cells, applied in a bioabsorbable matrix, for treatment of perianal fistulas in patients with Crohn's disease. Gastroenterology 153:59–62.e2
67. Le Cosquer G, Buscail E, Gilletta C, Deraison C, Duffas JP, et al. 2022. Incidence and risk factors of cancer in the anal transitional zone and ileal pouch following surgery for ulcerative colitis and familial adenomatous polyposis. Cancers 14:530
68. Yui S, Nakamura T, Sato T, Nemoto Y, Mizutani T, et al. 2012. Functional engraftment of colon epithelium expanded in vitro from a single adult Lgr5+ stem cell. Nat. Med. 18:618–23
69. Vergnolle N, Cirillo C. 2018. Neurons and glia in the enteric nervous system and epithelial barrier function. Physiology 33:269–80
70. Suenaert P, Bulteel V, Lemmens L, Noman M, Geypens B, et al. 2002. Anti–tumor necrosis factor treatment restores the gut barrier in Crohn's disease. Am. J. Gastroenterol. 97:2000–4
71. Vernia P, Annese V, Bresci G, d'Albasio G, D'Inca R, et al. 2003. Topical butyrate improves efficacy of 5-ASA in refractory distal ulcerative colitis: results of a multicentre trial. Eur. J. Clin. Investig. 33:244–48
72. Lorenz-Meyer H, Bauer P, Nicolay C, Schulz B, Purrmann J, et al. 1996. Omega-3 fatty acids and low carbohydrate diet for maintenance of remission in Crohn's disease. A randomized controlled multicenter trial. Scand. J. Gastroenterol. 31:778–85
73. Stremmel W, Ehehalt R, Autschbach F, Karner M. 2007. Phosphatidylcholine for steroid-refractory chronic ulcerative colitis: a randomized trial. Ann. Intern. Med. 147:603–10
74. El-Tawil AM. 2012. Zinc supplementation tightens leaky gut in Crohn's disease. Inflamm. Bowel Dis.

75. 18:e399
76. Sturniolo GC, Di Leo V, Ferronato A, D'Odorico A, D'Inca R. 2001. Zinc supplementation tightens "leaky gut" in Crohn's disease. Inflamm. Bowel Dis. 7:94–98
77. Simmons JD, Mullighan C, Welsh KI, Jewell DP. 2000. Vitamin D receptor gene polymorphism: association with Crohn's disease susceptibility. Gut 47:211–14
78. Lerner A, Matthias T. 2015. Changes in intestinal tight junction permeability associated with industrial food additives explain the rising incidence of autoimmune disease. Autoimmun. Rev. 14:479–89
79. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, et al. 2012. Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 491:119–24
80. de Lange KM, Moutsianas L, Lee JC, Lamb CA, Luo Y, et al. 2017. Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. Nat. Genet. 49:256–61
81. Sazonovs A, Stevens CR, Venkataraman GR, Yuan K, Avila B, et al. 2022. Large-scale sequencing identifies multiple genes and rare variants associated with Crohn's disease susceptibility. Nat. Genet. 54:1275–83