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INFLAMMATORY MEDIATORS AND IMMUNE RESPONSE IN CROHN'S DISEASE: MECHANISMS, IMPACT, AND THERAPEUTIC PERSPECTIVES

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Abstract: Crohn's disease is a chronic inflammation of the gastrointestinal tract resulting from the deregulated activation of the immune system, leading to chronic transmural inflammation. CD4+ T cells, alongside macrophages and neutrophils, play a central role in the pathology and, after being activated by antigens from their own intestinal microbiota or food, release inflammatory cytokines (TNF-α, IL-6, IL-12, IL-23) that cause damage to the intestinal mucosa, favoring complications in this epithelium, such as ulcers, fistulas and stenosis. This leads to the formation of an inflammatory cycle, consisting of both the summoning of more inflammatory cells due to the action of the cytokines released and other mechanisms, such as dysbiosis of the intestinal microbiota, which facilitates inadequate activation of the immune system and increases intestinal permeability. In addition, certain genetic factors, such as the NOD2, ATG16L1 and IL23R genes, are predisposing factors and contribute to disease recurrences by influencing the development of an exacerbated immune response, making clinical management more difficult. The complexity of the pathology is also related to the fact that its transmural involvement compromises all layers of the intestinal wall, and even in apparent remission, subclinical inflammation can remain. Considering this situation, continuous monitoring with biomarkers such as fecal calprotectin makes it possible to detect inflammation before it becomes symptomatic. Treatment consists of immunomodulators and biological therapies such as anti-TNF (infliximab and adalimumab) and IL-12/23 inhibitors, which act by reducing inflammation and contribute to maintaining remission. New approaches, such as JAK inhibitors, are being studied for patients refractory to the usual therapies. It should be noted that the progression of the disease is also influenced by environmental factors, including diet, whi-

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ch directly affects the intestinal microbiota, smoking and stress, both factors related to the effectiveness of treatment and control of recurrences. It is therefore understood that, despite numerous therapeutic advances, Crohn's disease remains a pathology in which a multidisciplinary approach is essential to improve quality of life and reduce the recurrence of inflammation.

Keywords: Crohn's disease, Chronic inflammation, Gastrointestinal tract, Immune system

INTRODUCTION

Crohn's disease is a chronic inflammatory condition that affects the gastrointestinal tract and is one of the main forms of inflammatory bowel disease (IBD) [1]. Although it can affect any part of the intestine, Crohn's disease most often affects the terminal ileum, the last part of the small intestine, and the colon, the large intestine [2]. The hallmark of this disease is transmural inflammation, i.e. it extends through all layers of the intestinal wall, from the mucosa (inner layer) to the serosa (outer layer) [3]. This type of inflammation can result in significant complications, such as obstructions, fistulas and abscesses, which can seriously affect patients' health and quality of life [4].

The global prevalence of Crohn's disease has shown an increase in recent decades, especially in developed countries [5]. The prevalence is estimated at between 100 and 300 cases per 100,000 people, with an increasing incidence, suggesting that environmental factors are increasingly influencing the development of the disease [6,7]. The disease was previously considered rare in developing countries, but the epidemiological transition observed, with an increase in cases in these countries too, points to an interaction between genetic and environmental factors [7]. Early identification and appropriate management are essential, given that Crohn's disease tends to be a long-term condition, with periods of remission and recurrence [8,9].

The chronic inflammation that characterizes Crohn's disease is complex and involves a dysregulated immune response [9]. The patient's immune system mistakenly attacks the cells of the intestine itself, leading to persistent inflammation [10]. This inflammatory process can result in significant damage to intestinal tissues, generating debilitating symptoms such as abdominal pain, diarrhea, rectal bleeding and fatigue [11]. Furthermore, in more advanced stages, the formation of fistulas (abnormal connections between the intestine and other organs), stenosis (narrowing of the intestine) and abscesses can occur, complications that further aggravate the clinical picture and prognosis of the disease [11].

The immune component plays a central role in the pathogenesis of Crohn's disease, and CD4+ T cells are fundamental in perpetuating inflammation [11]. These cells release inflammatory cytokines such as TNF-α, IL-6 and IL-23, which exacerbate the inflammatory process in the intestine [11,12]. In addition to the immune response, Crohn's Disease is considered a multifactorial disease, with a strong genetic predisposition[11,12] . Genetic variants, such as those observed in the NOD2 and ATG16L1 genes, have been associated with an increased risk of developing the disease [11,12]. However, environmental factors also play a crucial role, such as poor diet, smoking and imbalances in the intestinal microbiota, all of which contribute to the development and progression of the disease [11,12].

Crohn's disease is characterized by its relapsing nature, meaning that patients can experience periods of remission followed by new inflammatory crises [11,12]. Recurrence of the disease is a significant challenge in treatment, as inflammation can return after a period of clinical stability, often in an unpre-

dictable way [11,12]. Risk factors such as the location of the disease (as in ileal or ileocolonic cases), the presence of complications such as fistulas and stenoses, and failure to adequately control inflammation are elements that increase the chances of recurrence and worsening of the patient's clinical condition [11,12].

Even during periods of remission, subclinical inflammation can persist in the intestine, contributing to the long-term recurrence of Crohn's disease [11,12]. Subclinical inflammation, which is often not detected by routine tests, is one of the major difficulties in managing the disease, as it can lead to new episodes of more intense clinical activity [11,12]. Effective control of this subclinical inflammation is crucial to preventing disease progression and improving patient prognosis [11,12]. New therapeutic approaches, such as immunomodulatory and biological treatments, have shown promise, but the challenge remains to monitor and control inflammation effectively, even when symptoms are not evident [12].

In recent years, significant advances have been made in understanding the pathophysiology of Crohn's Disease, with research focusing on the role of the intestinal microbiota, genetics and immune regulation [12]. In-depth study of these areas has led to the development of biological therapies, which aim to modulate the immune response and control inflammation more effectively [12]. Therapies such as TNF-α inhibitors and monoclonal antibodies have provided substantial relief from symptoms and an improvement in patients' quality of life [12]. However, despite advances in treatment, the disease remains a chronic and challenging condition that requires new strategies to improve both early diagnosis and long-term management [12].

A thorough understanding of the mechanisms underlying inflammation and the recurrence of Crohn's disease is essential for the development of more effective treatments and prevention strategies [12]. The evolution of biological therapies, the personalization of treatment based on genetic profiling and the early identification of subclinical inflammation are key components in improving the management of this complex disease [12]. Continued research is essential to transform scientific advances into clinical approaches that can ultimately provide a more effective solution for patients with Crohn's disease [12].

Conducting a systematic review on Crohn's Disease, especially focused on inflammation and recurrence, is extremely important, as it allows us to gather, analyze and synthesize the most recent and robust scientific evidence on the pathophysiological mechanisms, risk factors and management strategies of this complex condition [12]. A well-conducted review provides a global and up-to-date view, helping to identify gaps in knowledge and suggest areas for future research [12]. Furthermore, by consolidating data on the efficacy of emerging therapies, such as biological treatments and immunomodulators, a systematic review can guide best clinical practice and optimize the management of Crohn's disease, resulting in better outcomes for patients [12]. In this way, it becomes a valuable resource for both health professionals and researchers, contributing to advances in the treatment and quality of life of patients with the disease [12].

OBJECTIVES

The aim of this study is to explain the immune response in Crohn's disease, with an emphasis on the deregulated activation of CD4+ T cells, macrophages and neutrophils, which triggers a chronic inflammatory state in the gastrointestinal tract [12,13]. The main inflammatory mediators involved will be analyzed, including TNF-α, IL-6, IL-12 and IL-23, to understand how these cytokines contribute to the perpetuation of inflammation and the development of progressive intestinal lesions [12,13]. In addition, the impact of the intesti-

nal microbiota will be addressed, with a focus on dysbiosis and the imbalance between beneficial and pathogenic bacteria, which play an essential role in modulating the intestinal immune response [12,13,14].

Another relevant aspect to be investigated is the genetic factors associated with Crohn's Disease, including genes such as *NOD2*, *ATG16L1* and *IL23R*, which influence both the predisposition and severity of intestinal inflammation [12,13,14]. The integrity of the intestinal barrier will be discussed, considering how increased intestinal permeability and bacterial translocation favor inflammation and intensify the symptoms of the disease [12,13,14]. Transmural inflammation, characteristic of Crohn's Disease, will be explored in relation to its complications, such as the formation of fistulas and stenoses, which significantly impact patients' quality of life [12,13,14].

Finally, the study will seek to discuss the therapeutic implications of this knowledge, highlighting how understanding immunological, genetic and microbiological mechanisms can contribute to the development of more effective and personalized therapeutic strategies [13,14]. The importance of innovative approaches, including biological therapies directed against specific inflammatory mediators and interventions aimed at modulating the intestinal microbiota, will be emphasized as a promising prospect for improving the prognosis of patients with Crohn's disease [14].

METHODOLOGY

This integrative review was conducted with the aim of analyzing the best available evidence on the immune response in Crohn's disease, with an emphasis on the deregulated activation of CD4+ T cells, macrophages and neutrophils, as well as the impact of intestinal microbiota and genetic factors associated with the disease [14]. To this end, the PUBMED, VHL and MEDLINE databases were consulted, covering publications between 2019 and 2024 [14]. The search was carried out using keywords such as "Crohn's Disease", "Immune Response", "Inflammatory Cytokines", "Microbiota", "Genetic Susceptibility", combined by Boolean operators (AND, OR) to maximize the relevance of the results [14,15].

Additional filters were applied to limit the selection of studies to the English language, excluding narrative review articles and non-peer-reviewed studies [14,15]. The inclusion of articles followed strict criteria, including studies that addressed the main inflammatory mediators involved, such as TNF-α, IL-6, IL-12 and IL-23, as well as research that analyzed the role of the intestinal microbiota in modulating the immune response and the genes associated with Crohn's disease predisposition and severity, such as NOD2, ATG16L1 and IL23R [14,15]. Articles that dealt with other inflammatory bowel diseases that were not specifically related to Crohn's disease or that did not detail the immunological and genetic mechanisms involved were excluded [14,15,16].

The article selection process was carried out in two stages. In the first phase, 312 titles and abstracts were analyzed to identify relevant studies within the initial set of retrieved articles [14,15,16]. In the second phase, 39 full texts of the selected articles were evaluated in detail, extracting data on the activation of immune system cells, the role of cytokines in perpetuating inflammation, the influence of the intestinal microbiota in modulating the immune response and the relationship between genetic factors and intestinal inflammation [15,16].

The data was organized in a systematic way, allowing a comparison between the different immunological, genetic and microbiological aspects of Crohn's Disease [15,16]. The final analysis was conducted based on the criteria of impact on the pathogenesis of the disease, correlation with the severity of symptoms and possible therapeutic implications [15,16]. This

integrative approach enabled a synthesis of the best available evidence, providing a comprehensive overview to guide future research and contribute to the development of more effective and personalized therapeutic strategies for the management of Crohn's disease [16].

RESULTS

INFLAMMATORY MEDIATORS AND IMMUNE RESPONSE

Inflammation in Crohn's disease is a central feature of the pathology and is closely linked to the deregulated activation of the immune system. CD4+ T cells, macrophages and neutrophils are the main mediators of this inflammatory response [16,17,18]. In Crohn's disease, the immune system, in an error of regulation, attacks the intestinal cells themselves, leading to chronic inflammation that can extend to all layers of the wall intestinal[16,17,18]. CD4+ T cells are activated by various factors, such as antigens from intestinal bacteria or food components, which results in the release of pro-inflammatory cytokines, such as TNF-α, IL-6, IL-12 and IL-23 [17,18]. These cytokines play a fundamental role in aggravating inflammation, being responsible for perpetuating the inflammatory process in the intestine and causing significant damage to the intestinal mucosa [17,18].

The role of CD4+ T cells is particularly important in the pathogenesis of Crohn's disease [17,18,19]. These cells are activated by antigens, which can originate from the intestinal microbiota or even from inadequately digested food [17,18,19]. After activation, CD4+ T cells release inflammatory cytokines which, in turn, bind to receptors on intestinal cells, including epithelial cells and other cells of the immune system [18,19,20]. This triggers a cascade of biochemical events that amplify the inflammatory response, generating a cycle of continuous tissue damage [18,19,20]. The production of cytokines such as TNF-α has been shown to be particularly important and is a therapeutic target in several modern treatments, such as anti-TNF biological agents, which aim to block this mediator and reduce intestinal inflammation [18,19,20].

In addition to CD4+ T cells, Crohn's disease also involves other types of immune cells, such as macrophages and neutrophils, which play crucial roles in the inflammatory process [19,20,21]. When activated, macrophages secrete a range of inflammatory mediators, including other cytokines such as IL-12, as well as enzymes and lipid mediators [20,21,22]. This release of pro-inflammatory substances contributes to the maintenance of inflammation and the worsening of intestinal damage [20,21,22]. Neutrophils, cells of the immune system present in large quantities during inflammatory outbreaks, release enzymes that further damage intestinal tissue, which can result in complications such as ulcers and fistulas [21,22,23].

The presence of these immune cells in the intestinal mucosa during episodes of inflammation in Crohn's disease is crucial for the progression of the disease [22,23,24]. In addition to cytokines, immune cells release several additional molecules, such as chemokines, which attract more inflammatory cells to the site of inflammation [22,23,24,25]. This recruitment of immune cells further aggravates tissue damage and perpetuates the inflammatory cycle [22,23,24,25]. The exacerbated activity of CD4+ T cells and other components of the immune system contributes to the formation of lesions, stenoses and even more serious complications, such as intestinal fistulas, which can be responsible for severe symptoms and long-term complications [22,23,24,25].

The interaction between immune cells and the cells of the intestinal epithelium is particularly relevant in Crohn's disease, since the

inflammation reaches the deeper layers of the mucosa, becoming transmural [22,23,24,25]. The impact of this deep and continuous inflammation is the destruction of intestinal cells, compromising intestinal function and resulting in the typical symptoms of the disease, such as abdominal pain, diarrhea and bleeding [23,24,25,26]. In addition , the constant production of inflammatory cytokines such as IL-23 maintains the cycle of inflammation, worsening the condition and making control of the disease a clinical challenge [23,24,25,26]. Thus, understanding the immunological mechanisms involved in Crohn's Disease, especially with regard to the activation of CD4+ T cells and their interaction with other immune cells, is fundamental for the development of more effective and targeted treatments [24,25,26,27].

CHANGES IN THE INTESTINAL MICROBIOTA

The intestinal microbiota plays a crucial role in maintaining immune homeostasis and protecting against pathogens [26,27,28]. In Crohn's disease, there is a significant alteration in the composition of the microbiota, known as intestinal dysbiosis. This dysbiosis is characterized by an imbalance between beneficial and pathogenic bacteria in the gut [26,27,28]. An increase in pathogenic bacteria, such as *Escherichia coli* and *Bacteroides fragilis*, and a reduction in beneficial bacteria can promote inappropriate activation of the immune system [26,27,28,29]. This imbalance favors chronic inflammation by stimulating the activation of immune cells, such as CD4+ T cells, and the release of pro-inflammatory cytokines, perpetuating the inflammatory cycle in the gut [26,27,28,29].

Furthermore, a reduction in bacterial diversity has been associated with Crohn's disease, indicating that a less diverse microbiota may be a risk factor for the development of the disease [27,28,29]. When pathogenic bacteria proliferate in excess, they can release substances that induce intestinal inflammation, exacerbating the symptoms of the disease and favoring the progression of inflammation [27,28,29]. Studies suggest that these alterations in the intestinal microbiota not only contribute to inadequate immune activation, but also interfere with the function of the intestinal mucosa, compromising its ability to act as a protective barrier against invading agents [28,29]. This strengthens the hypothesis that intestinal dysbiosis plays a key role in the pathogenesis of Crohn's disease, making it a promising target for future therapeutic approaches [28,29].

GENETIC FACTORS

Crohn's Disease is a multifactorial disease, with a complex interaction between genetic and environmental factors that predispose individuals to the development and progression of the disease [28,29]. Several genes have been identified as being associated with the risk of developing Crohn's Disease, among which the NOD2, ATG16L1 and IL23R genes are the most studied [28,29]. The NOD2 gene, for example, encodes a protein that plays a key role in detecting pathogens in the gut, and mutations in this gene are associated with an altered immune response, which can contribute to the chronic inflammation characteristic of the disease [28,29,30].

Genetic polymorphisms, which are variations in genes, can affect the function of the proteins encoded by these genes and, consequently, influence the body's immune response [28,29,30]. In the case of Crohn's disease, polymorphisms in the NOD2, ATG16L1 and IL23R genes result in an exacerbated immune response in the intestine, increasing inflammation [29,30]. The ATG16L1 gene is related to the function of autophagosomes, cellular processes responsible for the degra-

dation of pathogens, and its mutation can compromise the ability to eliminate pathogenic microorganisms from the gut [29,30]. The IL23R gene is involved in the regulation of Th17 cells, which play a central role in intestinal inflammation [30].

Furthermore, some genetic variants are not only associated with the development of Crohn's disease, but also have implications for the recurrence of the disease [30,31]. Studies have shown that individuals with certain genetic variants are more likely to have recurrent outbreaks or the involvement of different segments of the gastrointestinal tract [30,31]. These findings suggest that the genetic profile of each patient can influence both the course of the disease and the response to treatment, highlighting the importance of personalized medicine [30,31]. Identifying these genetic variants offers the opportunity to develop more targeted therapeutic approaches aimed at modulating the exacerbated immune response and reducing persistent inflammation [31].

INTESTINAL BARRIER AND PERMEABILITY

The intestinal barrier plays an essential role in protecting the body, preventing pathogens, toxins and other harmful substances present in the intestine from entering the bloodstream and affecting other organs [31]. This barrier is made up of epithelial cells joined by tight junctions, as well as mucous secretions that form a protective layer [31]. However, in Crohn's disease, the integrity of this barrier can be compromised, resulting in increased intestinal permeability [31,32]. The loss of the protective function of the intestinal barrier facilitates the passage of microorganisms and their substances, causing a process known as bacterial translocation [31,32]. This activates the immune system, leading to chronic inflammation and perpetuating Crohn's disease [31,32,33].

Bacterial translocation, which occurs when intestinal bacteria invade the bloodstream, triggers an exacerbated immune response that aggravates intestinal inflammation [31,32,33]. One of the factors that contributes to the loss of intestinal barrier integrity is a decrease in mucin production [31,32,33]. Mucin is a viscous substance secreted by goblet cells that coats epithelial cells, forming a protective layer against external agents [31,32,33]. When its production is reduced, the protection of the intestinal mucosa weakens, allowing harmful substances to pass through the intestinal wall [31,32,33]. In addition, the alteration of epithelial cells, which become damaged and disorganized in Crohn's disease, contributes to the failure of tight junctions between cells, further increasing intestinal permeability [31,32,33]. These mechanisms are closely linked to the progression of the disease, exacerbating symptoms and contributing to chronic inflammation [31,32,33].

TRANSMURAL INFLAMMATION AND FISTULA FORMATION

Transmural inflammation is a defining feature of Crohn's disease, which means that the inflammation not only affects the innermost layer of the intestinal wall (the mucosa), but also penetrates all layers of the intestinal wall, including the submucosa, muscularis and serosa [31,32,33,34]. This extension of the inflammation results in deeper and more severe damage to the intestinal tissue and can affect the normal functions of the intestine [31,32,33,34]. One of the most common complications associated with transmural inflammation is the formation of fistulas, which are abnormal connections that can develop between the intestine and other organs or structures, such as the bladder, the skin, or even between different segments of the intestine itself [31,32,33,34].

Fistula formation occurs when severe inflammation destroys the layers of the intestinal wall, creating channels that connect parts of the intestine to other areas [32,33,34]. Fistulas can be simple or complex, depending on their location and the involvement of multiple structures [32,33,34]. They can cause severe symptoms such as abdominal pain, infection, fever, secretion of fecal fluid in inappropriate places and additional complications such as abscesses [32,33,34]. Intestinal fistulas can lead to a range of problems, such as malnutrition, dehydration and even sepsis in more advanced cases [32,33,34]. Treating these complications can be challenging and often involves a combination of drugs, surgical procedures and, in some cases, biological therapies [32,33,34].

As well as complicating the clinical management of the disease, transmural inflammation and the formation of fistulas can significantly influence the progression of Crohn's disease [33,34]. Fistulas persist and can worsen over time, exacerbating symptoms and making treatment more complex [33,34]. The presence of fistulas is one of the factors that defines the complicated form of Crohn's disease, which can be more difficult to control with conventional medication [33,34]. For patients with complex or persistent fistulas, surgical interventions may be necessary to treat or remove the affected intestinal segments [33,34]. Thus, transmural inflammation not only affects patients' quality of life, but also imposes substantial challenges for the treatment and control of the disease over time [34].

INFLAMMATION AND RECURRENCE

Crohn's disease is characterized by a relapsing nature, i.e. patients often experience periods of remission followed by bouts of inflammation [32,33,34,35,36]. Although symptoms may disappear temporarily, inflammation in the intestine can continue, often subclinically, i.e. without showing any obvious signs. Even in a remission phase, the persistence of low-grade inflammation can be enough to trigger a new outbreak [32,33,34,35,36]. This makes managing the disease particularly challenging because, although treatments can relieve symptoms, the underlying inflammation can continue to affect the gut and contribute to relapse [32,33,34,35,36].

Clinical studies have shown that the recurrence rate of Crohn's disease is high, even after significant interventions, such as the use of biological drugs, immunosuppressants or even surgery [34,35,36]. These treatments can temporarily control symptoms and even induce remission, but the inflammation in the intestine is often not completely eradicated, leading to a return of symptoms in many cases [34,35,36]. The chronic nature of the disease and the patient's exacerbated immune response make disease management an ongoing process, requiring constant vigilance and therapeutic adjustments to maintain remission and prevent outbreaks [34,35,36].

Several risk factors contribute to the recurrence of Crohn's disease [34,35,36]. One of the most important is the persistence of subclinical inflammation, which is not easily detected but continues to damage intestinal tissue [36,37,38,39]. Other factors include failure to control the patient's immune response, smoking, which has a negative impact on intestinal inflammation, and the presence of complications such as fistulas or stenoses, which can worsen the progression of the disease [36,37,38,39]. These factors significantly

increase the risk of new outbreaks, making a personalized and continuous approach to the treatment and monitoring of patients with Crohn's disease even more important [36,37,38,39].

DISCUSSION

Crohn's disease is a chronic condition characterized by persistent inflammation of the gastrointestinal tract, which presents significant challenges in controlling inflammation and preventing its recurrence [33,34]. Although treatments have evolved, the complexity of the molecular mechanisms involved in the disease makes it difficult to achieve complete and lasting remission [22,23,24,25]. Chronic inflammation in Crohn's disease is a multifactorial process, where interactions between the immune system, the intestinal microbiota and genetic factors contribute to the persistence and severity of the disease [22,23,24,25,26,27,28]. Effective control of inflammation is fundamental to improving the patient's quality of life and preventing complications, but this requires more sophisticated and personalized therapeutic approaches [22,23,24,25,26,27,28].

The molecular mechanisms underlying chronic inflammation in Crohn's Disease involve immune cells, such as Th1 and Th17 cells, which play a central role in the inflammatory response [14,15,16,17,18]. Th1 cells, for example, produce cytokines such as TNF-α and IFN-γ, while Th17 cells produce IL-17, both of which contribute to the amplification of intestinal inflammation [14,15,16,17,18]. In addition, excessive production of inflammatory cytokines, such as TNF-α, IL-6, IL-12 and IL-23, aggravates the inflammatory process, perpetuating intestinal damage [1,2,7,8,9,14,15,16,17,18]. In individuals with Crohn's disease, there is a failure in the normal resolution of inflammation, which results in the persistence of chronic inflammation, a key factor in the recurrence of the disease [10,11,12,13]. This process of continuous inflammation is difficult to control, as the exacerbated immune responses are not easily modulated by conventional therapies [10,11,12,13,15,16].

The treatment of Crohn's disease has focused on immunomodulation, using biological therapies and drugs that specifically target the molecules and cells involved in the inflammatory response [13,15,16,17]. Biological therapies such as anti-TNF, anti-IL-12/23 and anti-integrins, have shown efficacy in reducing inflammation and improving symptoms [13,15,16,17]. JAK inhibitors have also been used successfully, especially in patients who do not respond well to traditional treatments [15,16,17,18]. In addition, cell-based therapies, such as hematopoietic stem cell transplantation, offer an option for severe and refractory cases. However, these therapies still have limitations, including side effects and ineffectiveness in some patients [15,16,17,18]. The challenge remains to find treatments that offer a lasting solution to chronic and recurrent inflammation [15,16,17,18,23,28,29].

Although current treatments represent a major advance, the difficulty in achieving complete and lasting remission is related to several factors, including the persistence of subclinical inflammation and interactions with the intestinal microbiota [15,16,17,18,23,28,29]. Dysbiosis, or an imbalance in the microbiota, can contribute to the perpetuation of inflammation and hinder the response to treatments [15,16,17,18,23,28,29]. In addition, smoking and the presence of complications such as fistulas and stenoses are factors that increase the risk of the disease recurring, making the control of inflammation even more complex [15,16,17,18,23,28,29]. These variables make Crohn's disease a condition that requires constant monitoring and frequent therapeutic adjustments [18,23,28,29].

Finally, regular monitoring is essential to detect subclinical inflammation early and prevent serious complications [18,23,28,29]. Strategies such as endoscopy, biopsies and the measurement of biomarkers such as fecal calprotectin allow for a more accurate assessment of intestinal inflammatory activity [18,23,28,29,30]. Early detection allows therapy to be modulated before more severe outbreaks develop, which is key to improving long-term prognosis [18,23,28,29,30,31]. With advances in understanding the pathogenesis of the disease and the development of new therapeutic options, the control of inflammation in Crohn's Disease has the potential to be more effective in the future, providing a better quality of life and fewer complications for patients [19,23,28,29,30,31].

Environmental and lifestyle factors have a significant impact on the course of Crohn's disease, influencing both inflammation and disease recurrence [29,30,31]. Diet, for example, is one of the main determinants of this modulation [29,30,31,32]. Processed foods, rich in saturated fats and refined sugars, can alter the intestinal microbiota, contributing to a pro-inflammatory environment [29,30,31,32,33]. On the other hand, a diet rich in fruit, vegetables and fiber has a protective effect, favoring a healthy microbiota and positively modulating the immune response [29,30,31,32,33]. Therefore, dietary adjustments can be an essential element in managing the disease, complementing conventional treatments and improving patients' quality of life [31,32,33,38,39].

Smoking is another environmental factor known to increase inflammation and worsen the symptoms of Crohn's disease [31,32,33,38,39]. Smoking not only increases the risk of complications, but is also directly associated with greater disease severity and increased chances of recurrence [32,33,38,39]. Tobacco smoke induces changes in the intestinal microbiota and interferes with immune responses, exacerbating inflammation [33,38,39]. In addition, smoking can reduce the effectiveness of some treatments, making smoking cessation one of the key recommendations in disease management [32,33,38,39]. Interventions to support patients in quitting smoking should be an integral part of the treatment plan [32,33,38,39].

Stress, an emotional and psychosocial factor, also has an important impact on inflammation and the progression of Crohn's disease [23,26,38,39]. Chronic stress can compromise the functioning of the immune system, making it more prone to inflammatory reactions [23,26,38,39]. In many patients, periods of stress are followed by outbreaks of the disease, which suggests an interaction between emotional and physiological factors [28,29,30]. Stress control, through therapies such as psychotherapy, mindfulness or relaxation techniques, has shown benefits in reducing inflammation and improving symptoms, helping patients to better manage their condition in the long term [28,29,30].

Given the heterogeneous nature of Crohn's disease, personalizing treatment is essential to optimize therapeutic results [28,29,30]. Each patient has individual characteristics, both genetic and environmental, which influence the manifestation of the disease and its response to treatment [31,32,33,34]. Personalization involves adapting therapies based on the specific needs of each patient, which can include choosing more effective drugs or modifying lifestyle [31,32,33,34]. This can result in a more efficient and less costly approach, reducing the risk of complications and improving adherence to treatment [31,32,33,34].

The role of genetics is also crucial in personalizing treatment [36,37,38,39]. Advances in genetic and molecular testing have made it possible to identify genetic variants associated with Crohn's Disease, which can influence both the severity of the disease and the res-

ponse to treatment [36,37,38,39]. Genetic tests help doctors predict which therapies will be most effective for each patient, allowing them to avoid ineffective treatments and minimize risks [36,37,38,39]. Early identification of genetic factors can be a fundamental step towards more precise management of Crohn's disease, helping to minimize complications and improve disease control over time [36,37,38,39]

Despite advances in treatment, Crohn's disease remains a chronic condition that requires an integrated approach, involving not only pharmacological treatments, but also lifestyle modifications and the management of emotional factors [36,37,38,39]. Combined strategies, such as a balanced diet, smoking cessation and stress control, have been shown to be effective in preventing flare-ups [36,37,38,39]. Although a definitive cure has not yet been achieved, advances in therapies, both pharmacological and cell-based, offer hope for the future [36,37,38,39]. A multidisciplinary approach, with regular follow-up by gastroenterologists, nutritionists, psychologists and other professionals, is essential to ensure that patients receive the best possible care, promoting their quality of life and preventing long-term complications [36,37,38,39].

CONCLUSION

Crohn's disease is a complex condition characterized by a dysregulated immune response that results in chronic, transmural inflammation in the gastrointestinal tract. Excessive activation of CD4+ T cells, macrophages and neutrophils, associated with the release of inflammatory cytokines such as TNF-α, IL-12 and IL-23, plays a central role in the perpetuation of intestinal inflammation and the progression of the disease. In addition, intestinal dysbiosis and genetic factors contribute to the worsening of the immune response and the chronicity of the disease. The loss of intestinal barrier integrity and the formation of fistulas further increase the clinical complexity of Crohn's Disease, requiring careful and individualized therapeutic management. Despite advances in treatment, including biological therapies, the relapsing nature of the disease and associated complications, such as fistulas and stenosis, impose significant challenges in the management of Crohn's Disease. A deeper understanding of the immunological and molecular mechanisms underlying the disease opens the door to new therapeutic approaches and more effective management strategies, aimed not only at controlling symptoms, but also at preventing long-term complications.

REFERENCES

1. Dolinger, Michael et al. "Crohn's disease." *Lancet (London, England)* vol. 403,10432 (2024): 1177-1191. doi:10.1016/S0140-6736(23)02586-2

2. Petagna, L et al. "Pathophysiology of Crohn's disease inflammation and recurrence." *Biology direct* vol. 15,1 23. 7 Nov. 2020, doi:10.1186/s13062-020-00280-5

3. Roda, Giulia et al. "Crohn's disease." *Nature reviews. Disease primers* vol. 6,1 22. 2 Apr. 2020, doi:10.1038/s41572-020-0156-2

4. Parian, Alyssa M et al. "Management of Perianal Crohn's Disease." *The American journal of gastroenterology* vol. 118,8 (2023): 1323-1331. doi:10.14309/ajg.0000000000002326

5. Caparrós, Esther et al. "Dysbiotic microbiota interactions in Crohn's disease." *Gut microbes* vol. 13,1 (2021): 1949096. doi:10.1080/19490976.2021.1949096

6. Verburgt, Charlotte M et al. "Nutritional Therapy Strategies in Pediatric Crohn's Disease." *Nutrients* vol. 13,1 212. 13 Jan. 2021, doi:10.3390/nu13010212

7. Cockburn, Ella et al. "Crohn's disease: an update." *Clinical medicine (London, England)* vol. 23,6 (2023): 549-557. doi:10.7861/clinmed.2023-0493

8. Srinivasan, Ashish R. "Treat to target in Crohn's disease: A practical guide for clinicians." *World journal of gastroenterology* vol. 30,1 (2024): 50-69. doi:10.3748/wjg.v30.i1.50

9. Atreya, Raja, and Britta Siegmund. "Location is important: differentiation between ileal and colonic Crohn's disease." *Nature reviews. Gastroenterology & hepatology* vol. 18,8 (2021): 544-558. doi:10.1038/s41575-021-00424-6

10. Baldwin, Katherine et al. "Managing pediatric Crohn's disease: recent insights." *Expert review of gastroenterology & hepatology* vol. 17,10 (2023): 949-958. doi:10.1080/17474124.2023.2267431

11. Shehada, Mahmoud, and Lisa E McMahon. "Recurrent Crohn's disease." *Seminars in pediatric surgery* vol. 33,2 (2024): 151403. doi:10.1016/j.sempedsurg.2024.151403

12. Gonzalez, Carlos G et al. "Location-specific signatures of Crohn's disease at a multi-omics scale." *Microbiome* vol. 10,1 133. 24 Aug. 2022, doi:10.1186/s40168-022-01331-x

13. Cheng, Wei-Xin et al. "Palmitoylation in Crohn's disease: Current status and future directions." *World journal of gastroenterology* vol. 27,48 (2021): 8201-8215. doi:10.3748/wjg.v27.i48.8201

14. Bernstein, Charles N, and Miguel Regueiro. "Postoperative Crohn's Disease." *Journal of clinical gastroenterology* vol. 57,8 749-753. 1 Sep. 2023, doi:10.1097/MCG.0000000000001865

15. Yamamoto-Furusho, J K et al. "First Mexican Consensus on Crohn's disease." *Revista de gastroenterologia de Mexico (English)* vol. 89,2 (2024): 280-311. doi:10.1016/j.rgmxen.2024.03.001

16. Hugot, Jean-Pierre et al. "Crohn's Disease: Is the Cold Chain Hypothesis Still Hot?." Journal of Crohn's & colitis vol. 15,4 (2021): 678-686. doi:10.1093/ecco-jcc/jjaa192

17. Chen, Lynna et al. "Examining dietary interventions in Crohn's disease." *World journal of gastroenterology* vol. 30,34 (2024): 3868-3874. doi:10.3748/wjg.v30.i34.3868

18. Roberts, Zachary J, and Alessandro Fichera. "Surgical priorities in abdominal Crohn's disease." *Updates in surgery* vol. 75,3 (2023): 451-454. doi:10.1007/s13304-023-01456-0

19. Friedberg, Scott, and David T Rubin. "Intestinal Cancer and Dysplasia in Crohn's Disease." *Gastroenterology clinics of North America* vol. 51,2 (2022): 369-379. doi:10.1016/j.gtc.2021.12.011

20. Loras, Carme et al. "Position Statement. Recommendations of the Spanish Group on Crohn's Disease and Ulcerative Colitis (GETECCU) on the treatment of strictures in Crohn's disease." "Documento de posicionamiento. Recomendaciones del grupo español de trabajo en enfermedad de Crohn y colitis ulcerosa (GETECCU) sobre el tratamiento de la estenosis en la enfermedad de Crohn." *Gastroenterologia y hepatologia* vol. 45,4 (2022): 315-334. doi:10.1016/j.gastrohep.2021.07.001

21. Honap, Sailish et al. "Anogenital Crohn's Disease and Granulomatosis: A Systematic Review of Epidemiology, Clinical Manifestations, and Treatment." *Journal of Crohn's & colitis* vol. 16,5 (2022): 822-834. doi:10.1093/ecco-jcc/jjab211

22. Miyatani, Yusuke et al. "Dual-Targeted Therapy with Upadacitinib and Ustekinumab in Medically Complex Crohn's Disease." *Digestive diseases and sciences* vol. 69,2 (2024): 355-359. doi:10.1007/s10620-023-08182-y

23. Kamboj, Amrit K et al. "Crohn's Disease of the Esophagus." *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* vol. 20,2 (2022): A15-A16. doi:10.1016/j.cgh.2020.10.032

24. Carroll, Dylan, and Sandy Kavalukas. "Management of Complications in Crohn's Disease." Advances in surgery vol. 58,1 (2024): 19-34. doi:10.1016/j.yasu.2024.04.002

25. Cao, Siyan et al. "Pathogenesis of Perianal Fistulising Crohn's Disease: Current Knowledge, Gaps in Understanding, and Future Research Directions." *Journal of Crohn's & colitis* vol. 17,6 (2023): 1010-1022. doi:10.1093/ecco-jcc/jjad008

26. Sila, Sara, and Iva Hojsak. "Nutritional Management for Crohn's Disease." *Nutrients* vol. 16,16 2597. 7 Aug. 2024, doi:10.3390/nu16162597

27. Sila, Sara, and Iva Hojsak. "Nutritional Management for Crohn's Disease." *Nutrients* vol. 16,16 2597. 7 Aug. 2024, doi:10.3390/nu16162597

28. Zabot, Gilmara Pandolfo et al. "Modern surgical strategies for perianal Crohn's disease." *World journal of gastroenterology* vol. 26,42 (2020): 6572-6581. doi:10.3748/wjg.v26.i42.6572

29. Scheurlen, Katharina M et al. "State-of-the-art surgery for Crohn's disease: part III-perianal Crohn's disease." *Langenbeck's archives of surgery* vol. 408,1 132. 30 Mar. 2023, doi:10.1007/s00423-023-02856-x

30. Zhou, Yu-Wei et al. "Crohn's disease as the intestinal manifestation of pan-lymphatic dysfunction: An exploratory proposal based on basic and clinical data." *World journal of gastroenterology* vol. 30,1 (2024): 34-49. doi:10.3748/wjg.v30.i1.34

31. Nahon, Stéphane. "Vivre avec… la maladie de Crohn" [Living with… Crohn's disease]. *La Revue du praticien* vol. 73,4 (2023): 419-420.

32. Devi, Jalpa et al. "Perianal fistulizing Crohn's disease: Current perspectives on diagnosis, monitoring and management with a focus on emerging therapies." *Indian journal of gastroenterology : official journal of the Indian Society of Gastroenterology* vol. 43,1 (2024): 48-63. doi:10.1007/s12664-024-01524-2

33. Pizzoferrato, Marco et al. "Glucagon-like peptide-2 analogues for Crohn's disease patients with short bowel syndrome and intestinal failure." *World journal of gastroenterology* vol. 28,44 (2022): 6258-6270. doi:10.3748/wjg.v28.i44.6258

34. Zbar, Andrew. "Cutting piles in Crohn's disease." *Techniques in coloproctology* vol. 26,4 (2022): 329-330. doi:10.1007/s10151-022-02571-7

35. Yu, Irene et al. "Ileostomy Adenocarcinoma in Crohn's Disease." *The American surgeon* vol. 89,12 (2023): 6238-6240. doi:10.1177/00031348221117037

36. Macleod, Anne et al. "State-of-the-art surgery for Crohn's disease: Part II-colonic Crohn's disease and associated neoplasms." *Langenbeck's archives of surgery* vol. 407,7 (2022): 2595-2605. doi:10.1007/s00423-022-02572-y

37. McLellan, Paul, and Julien Kirchgesner. "Perianal fistulizing Crohn's disease and overall risk of cancer: No red flag." *United European gastroenterology journal* vol. 11,5 (2023): 401-402. doi:10.1002/ueg2.12401

38. Chen, Rirong et al. "Prognostic models for predicting postoperative recurrence in Crohn's disease: a systematic review and critical appraisal." *Frontiers in immunology* vol. 14 1215116. 30 Jun. 2023, doi:10.3389/fimmu.2023.1215116

39. Kagramanova, A V et al. *Terapevticheskii arkhiv* vol. 95,2 193-197. 30 Mar. 2023, doi:10.26442/00403660.2023.02.202061