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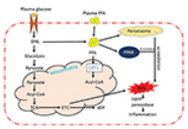

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REVIEW

Epithelial barrier dysfunction and microbial dysbiosis: exploring the pathogenesis and therapeutic strategies for Crohn's disease

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ABSTRACT

Crohn's disease (CD), a chronic gastrointestinal inflammatory disease, is becoming more widespread worldwide. Crohn's disease is caused by gut microbiota changes, genetics, environmental stresses, and immunological responses. Current treatments attempt to achieve long-term remission and avoid complications, delaying disease progression. Immunosuppressive measures and combination medicines should be started early for high-risk patients. These medicines monitor inflammatory indicators and adjust as needed. The epithelial barrier helps defend against physical, chemical, and immunological threats. When tissues' protective barrier breaks down, the microbiome may reach the layer underneath. Unbalanced microbial populations and inflammation impair healing and adjustment. Inflammatory cells infiltrating sensitive tissues aggravate the damage and inflammation. This approach promotes chronic inflammatory diseases. The epithelial barrier hypothesis states that hereditary and environmental variables cause epithelial tissue inflammation. This review focuses on how epithelial barrier break-down and microbial dysbiosis cause Crohn's disease and current advances in understanding the epithelial barrier, immune system, and microbiome. Additionally, investigate treatments that restore barrier integrity and promote microbial balance. Overall, it stresses the role of epithelial barrier failure and microbial dysbiosis in Crohn's disease development and discusses current advances in understanding the barrier, immunological responses, and microbiota.

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Introduction

A persistent inflammatory disorder of the gastrointestinal tract known as Crohn's disease (CD) is characterized by recurrent episodes of relapse and remission.[1] It affects the terminal ileum and colon, though it can involve any part of the gastrointestinal tract.[2] Inflammation in CD is typically segmental, asymmetrical, and transmural.[3] Initially, most patients present with an inflammatory phenotype, but half develop complications such as strictures, fistulas, or abscesses over time, often requiring surgical intervention.[4] Current therapeutic strategies focus on achieving deep and sustained remission, primarily preventing complications and arresting disease progression.[5–7]

The crucial role of the epithelial barrier in maintaining homeostasis and overall health. A variety of environmental and biological factors, such as allergens like house dust mites and pollen, as well as disease-causing microbes like bacteria, fungus, and viruses, may weaken the structural integrity of this barrier.[8] These stimuli may initiate inflammatory responses that disturb the tight junctions between epithelial cells, which are essential for preserving the functional integrity of the barrier. Crohn's disease is characterized by chronic inflammation that compromises the integrity of the intestinal barrier, facilitating the movement of luminal substances, such as bacteria, into the submucosa. The impairment of barrier function increases immune responses and sustains a loop of inflammation and tissue injury.[9]

A crucial factor contributing to this barrier dysfunction is gut microbiota composition. The microbiota refers to the varied microorganisms that inhabit the human gastrointestinal system, such as bacteria, archaea, fungi, and viruses. These bacteria are essential for preserving the integrity of the host's epithelial barrier, regulating metabolism, and maintaining immunological balance. However, in the case of Crohn's disease, there is often an imbalance in the microbial population, known as dysbiosis, which is strongly associated with the development of the

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illness. Imbalances in the bacterial population can disrupt the delicate balance between helpful and harmful bacteria, leading to increased inflammation in specific areas and contributing to illness progression.

The interaction between intestinal mucus and tight junctions efficiently blocks the spread of bacteria and reduces the risk of inflammation.[9] The breakdown of this protective barrier in the intestines shows the need for methods that increase mucus production and tight junction integrity to lower inflammation and keep the intestines' lining in balance.[10] These strategies are crucial for diminishing inflammation and maintaining the equilibrium of the intestinal lining.[3]

This review aims to clarify how epithelial barrier dysfunction and microbial dysbiosis contribute to the development of Crohn's disease. It will investigate recent progress in understanding the interactions between the epithelial barrier, immune responses, and the microbiota. Additionally, it highlights potential therapeutic strategies designed to restore barrier integrity and rebalance the microbial community. Through this exploration, it will seek to provide a thorough overview of the current and emerging approaches to treating Crohn's disease.

Pathogenesis of Crohn's disease

Crohn's disease is increasing due to genetic predisposition and various complex interactions.[11] Additionally, it can be associated with environmental factors, altered gut microbiota, and the disruption of homeostasis in innate and adaptive immune systems.[12] It is typically more common in young patients, presenting with symptoms such as abdominal pain, chronic diarrhea, weight loss, and fatigue.[13]

Crohn's disease is characterized by the formation of inflammation affecting the gastrointestinal tract, most commonly involving the distal ileum. Patients with Crohn's disease frequently experience flare-ups and recurrences.[14] The inflammation during the disease process and other triggering factors can lead to dysregulation of the immune system and subsequent disruption of the intestinal mucosa.[15]

Crohn's disease development is linked to tissue inflammation and an abnormal immune response to bacterial antigens in the luminal region.

Immune-mediated pathogenesis of Crohn's disease

CD's are characterized by a dysregulated immune response leading to ongoing gastrointestinal tract inflammation. CD development involves an intricate interaction between genetic susceptibility, environmental factors, and a modified gut microbiota.[16] This results in an uncontrolled immune response against luminal bacterial antigens.[17] In CD patients, a dysregulation of various immune system components is invariably found, with a pronounced hyperactivity of T cells. Excessive production of cytokines such as IL-12 and IFN-γ results in a Th-1 lymphocytic phenotype, which differs from the Th-2 phenotype seen in ulcerative colitis[18] (Figure 1).

Treatment for CD significantly alters the distribution and function of memory T (T_m) cell subsets. Macpherson et al.[19] conducted a study on patients with CD and observed a significant increase in the quantity of $CD8^+$ T cells in their peripheral blood mononuclear cells (PBMCs) after therapy. There were also changes in the numbers of $CD4^+$ and $CD8^+$ T cells in their mesenteric lymph nodes. People who have been conventionally treated have memory T cells that make less of the cytokines IFN-γ and TNF-α. Their immune system responds less to inflammation.[20] In mesenteric lymph node (MLN) lesions, fewer CD8+ stem cell-like memory T (Tscm) cells make IFN-γ. On the other hand, there are more $CD4^+$ T_{scm} cells and tissue-resident memory T (T_{rm}) cells in the intestinal mucosa.

Innate immune cells such as $CD14^+$ monocytes, natural killer cells, and various subsets of innate lymphoid cells (ILCs) are also involved in the pathogenesis of CD. ILCs, distinct from T and B cells, play a critical role in immune defense, inflammation, and tissue remodeling. They provide host defense against infections and initiate repair processes to restore and maintain homeostasis.[21] However, ILCs undergo alterations in CD that contribute to the disease's pathogenesis. ILC3s are especially flexible and can change their roles to be more pro-inflammatory in an inflammatory environment like in CD.[22]

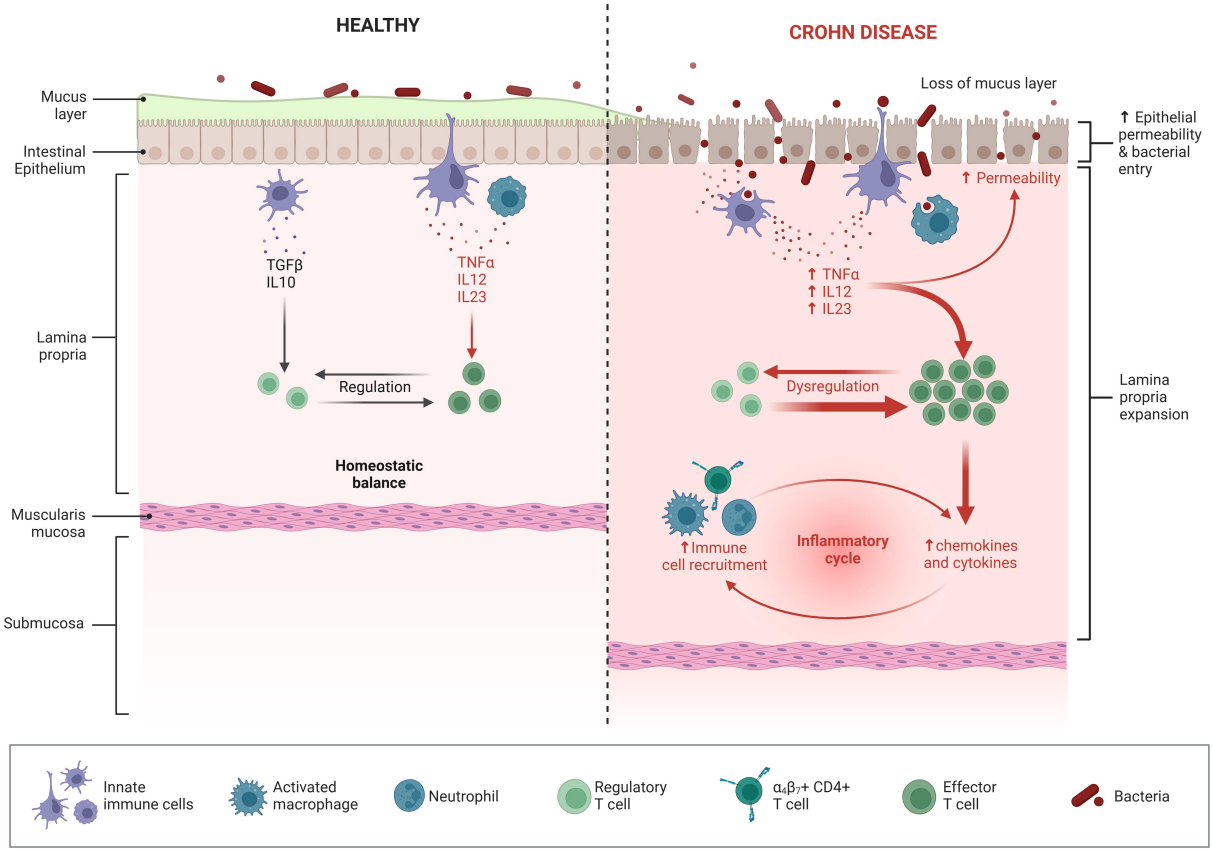

Figure 1. Pathogenesis of Crohn's disease. Compares healthy intestinal mucosa with those affected by Crohn's disease (CD). An intact mucus layer and regulatory cytokines like tgf-β and IL-10 maintain homeostasis in healthy mucosa. In CD, the loss of the mucus layer increases epithelial permeability and bacterial entry, leading to immune dysregulation. Elevated tnf-α, IL-12, and IL-23 levels promote excessive immune cell recruitment and a chronic inflammatory cycle. The CD is characterized by a hyperactive Th-1 lymphocytic response, differing from the Th-2 phenotype in ulcerative colitis, and results from interactions between genetic, environmental, and microbial factors.

The dysregulation of adaptive immune responses, characterized by an imbalance in pro-inflammatory cytokines like TNF-α, IL-12, IL-23, and IL-34, sets the stage for disease onset and progression[23,24] (Table 1). Similarly, the activation of innate immune pathways, including the stimulation of group 2 innate lymphoid cells (ILC2s) and Th2 cells by alarmins, leads to the secretion of IL-4, IL-5, and IL-13, promoting type 2 inflammation characterized by eosinophils, basophils, and mast cells. Furthermore, environmental factors such as air pollution trigger pro-inflammatory transcription factors (MAPKs, NF-κB), exacerbating inflammatory and immune responses. The alteration of the extracellular matrix (ECM) is also crucial in the progression of Crohn's disease (CD).[25] Matrix metalloproteinases (MMP-1 and MMP-3) facilitate the degradation of the extracellular matrix (ECM).[26] This mechanism facilitates tissue plasticity and promotes cellular migration toward inflamed regions.[27] The dysregulation of cytokines leads to the recruitment and activation of inflammatory cells, perpetuating the inflammatory process.[28] Various inflammatory mediators, including MADCAM-1 and integrin α4β4, generate further inflammatory mediators.[25] This process enhances leukocyte attachment and movement inside the tissue, intensifying inflammation.[26] Changes in the extracellular matrix (ECM) and inflammatory mediators have a complicated relationship that shows how complicated CD is and points out possible therapeutic targets for managing the disease.[28]

Epithelial barrier dynamics

Chronic inflammation and mucosal damage in Crohn's disease (CD) stem from an aberrant immune response against the gut microbiota. This

Table 1. Immune dysregulation in Crohn's disease.

1. Dysregulated Immune Response	Ongoing gastrointestinal inflammation	
	Interaction of genetic susceptibility, environmental factors, and modified gut microbiota	
	Uncontrolled immune response against luminal bacterial antigens	
2. Affected Cells	A. T Cells	Hyperactivity of T cells
		Excessive production of cytokines such as IL-12 and IFN-γ
		TH1 lymphocytic phenotype
	B. Memory T (Tm) Cells	Changes in distribution and function
		Increase in CD8+ T cells in peripheral blood mononuclear cells (PBMCs) after therapy
		Changes in CD4+ and CD8+ T cells in mesenteric lymph nodes (MLNs)
		Fewer CD8+ stem cell-like memory T (Tscm) cells in MLNs
		More CD4+ Tscm cells and tissue-resident memory T (Trm) cells in the intestinal mucosa
	C. Innate Immune Cells	CD14+ monocytes
		Natural killer cells
		Innate lymphoid cells (ILCs) ILC3s become more pro-inflammatory in CD
3. Cytokine Changes	Increased IL-12, IFN-γ, TNF-α, IL-23	
	Decreased IFN-γ and TNF-α in memory T cells after treatment	
4. Genetic and Environmental Factors	A. Genetic Factors	Genetic predispositions affect barrier function, microbial defense, and immune regulation
		Genetic alterations in MUT2 and FUT2 genes affecting epithelial barrier integrity
	B. Environmental Factors	Environmental factors: diet, smoking, infections
5. Extracellular Matrix (ECM) Alterations	Matrix metalloproteinases (MMP-1 and MMP-3) degrade ECM	
	Facilitates tissue plasticity and cellular migration	
	Recruitment and activation of inflammatory cells perpetuating inflammation	
	Inflammatory mediators: MADCAM-1, integrin α4β4	
	Changes in ECM and inflammatory mediators	

disruption in the normal activity of immune cells in the intestines results in prolonged inflammation and continuous harm to the intestinal lining. Understanding these pathways is crucial for developing targeted therapies that control the immune response, restore mucosal integrity, and sustain long-term remission in CD patients. Additionally, CD is characterized by genetic alterations in the MUT2 and FUT2 genes, which are vital for maintaining the integrity of the epithelial barrier. These genetic defects compromise the epithelium, allowing greater penetration of pathogens and weakening the body's natural defenses.[29]

These genetic and immune dysfunctions in CD patients highlight the critical role of maintaining epithelial integrity. In parallel, several researchers attribute the recent increase in chronic non-communicable conditions, such as autoimmune and allergy disorders, to environmental factors. Several researchers attribute the recent increase in chronic non-communicable conditions, such as autoimmune and allergy disorders, to environmental factors. These disorders can harm the protective layer of cells called the epithelial barrier.[8] Airborne pollutants like cigarette smoke, particulate matter, and volatile organic compounds can negatively affect the epithelial barrier. Allergens such as peanuts, eggs, milk, house dust mites, and pollen, as well as micro- and nano-plastics and food additives like sweeteners, colorants, and emulsifiers, may cause allergic reactions.[30] The disruption is exacerbated by the altered microbiome, imbalanced microbial composition, and resulting immune system activation (Environmental and health implications of air pollution: a review, 2020; UK Biobank project, 2019).

These environmental factors disrupt the microbiome and immune system and directly impact the epithelial barrier's structural integrity. The intercellular tight junction (TJ) proteins in the apical region of epithelial cells are crucial for maintaining this barrier. The intercellular tight junction (TJ) proteins in the apical region of epithelial cells are crucial for maintaining this barrier. Transmembrane proteins like occluding (OCLN) and claudins (CLDNs) are important TJ proteins. Intracellular plaque proteins like zonula occludens (ZO-1) are also involved. These proteins engage with both transmembrane proteins and the cytoskeleton to form a multiprotein complex that controls the transportation of molecules. These TJ proteins keep the epithelial barrier strong and working properly. This barrier helps keep harmful chemicals and pathogens out.[9,10]

These tight junction proteins maintain the epithelial barrier's structural integrity and regulate its permeability. The function of claudins is crucial in determining the permeability characteristics of tight junctions. Claudin family members can form

tight junction strands that exhibit various permeability properties.[31] This allows them to finely regulate their barrier functions according to specific needs.[31] Members of the claudin family can work together to create tight junction strands with different permeability levels. The expression and function of tight junction proteins can be influenced by various signaling pathways and environmental factors.[32] As a result, the regulation of tight junctions has changed.[32] Proteins are crucial in enhancing the barrier's integrity by controlling tight junctions.

Chronic inflammation of the intestinal mucosa in Crohn's disease (CD) is primarily a result of an abnormal immune response. The intestinal epithelium is crucial in maintaining a barrier between the gut contents and the underlying tissue.[31] In addition, it plays an important role in identifying and responding to microbial signals. Pattern recognition receptors (PRRs), including toll-like receptors (TLRs) and nucleotide-binding oligomerization domains (NLRs)-like receptors (NLRs), play a role in this process. The main role of these receptors is to identify pathogen-associated molecular patterns (PAMPs) and microbial metabolites. Afterward, they trigger immune responses that help maintain balance in the gastrointestinal tract. Compromised barrier function and the initiation of CD can occur when these pathways are disrupted.[32,33]

A significant issue arises from the increased permeability of the epithelium layer, allowing germs and pathogens to easily enter the subepithelial tissues. This results in prolonged inflammation and an unbalanced immune response.

Treatment of Crohn disease

Although there is no definitive cure for Crohn's disease, treatment algorithms highlight differences in managing mild to severe cases. The first step in treating Crohn's disease involves assessing whether the patient has perianal disease.[34] Treatment approaches use personalized therapy combinations tailored to the patient's condition and response. Continuous imaging and monitoring are essential for enhancing treatment effectiveness. New treatment combinations aim to maintain remission, improve the patient's quality of life, and prevent complications associated with Crohn's disease.[35,36]

The management of Crohn's disease has greatly improved with novel therapies and strategic approaches. In the past, the available choices for treatment were restricted, consisting of 5-aminosalicylates, repeated courses of corticosteroids, and immunomodulators.[37] As a result, there was a rise in the number of surgical removals of the intestines and the occurrence of difficulties caused by the extended use of corticosteroids.[38] Consequently, there was an increase in morbidity and a decline in the efficacy of healthcare interventions for persons.[39–43]

The development of biological medicines has represented substantial progress in managing Crohn's disease, considering the existing obstacles. Initiating biological therapy at an early stage of the illness is more effective, leading to greater remission rates in persons with shorter durations of the condition. Nevertheless, the absence of verified biomarkers presents a difficulty in identifying individuals who might gain advantages from early intensive treatment.

Medical management

The recent introduction of new medical advancements has significantly increased the treatment options available for Crohn's disease. This allows for a personalized approach considering the patient's unique illness characteristics, other medical conditions, lifestyle, and relevant medicine-related factors. Furthermore, individuals must receive proper guidance regarding therapy goals and protocols for monitoring their progress. As part of this comprehensive approach, it is essential to explore the role of antibiotics, corticosteroids, immunomodulators, anti-TNF therapy, alternative pathway therapies, and stem cell-based treatments, including the promising potential of MSC-derived extracellular vesicles, in effectively managing Crohn's disease (Table 2).

Antibiotics

It is advisable to use antibiotics to treat abscesses in the perianal and intra-abdominal areas that are associated with Crohn's disease.[44] However, it is not advisable to use them to treat luminal sickness or as the sole therapy for complex fistulizing disease.[45] The combination of ciprofloxacin and

Table 2. Treatments of Crohn's disease.

Treatment Option	Description	Indications	Risk/Considerations	Effectiveness
Antibiotics	Used to treat abscesses in perianal and intra-abdominal areas	Perianal disease, abscesses	Not recommended for luminal disease	Effective in combination with anti-TNF for perianal fistulas
Corticosteroids	Systemic and localized steroids for moderate to severe disease	Moderate to severe disease	Long term use risks (osteoporosis, diabetes)	Effective for inducing remission, goal ise steroid free remission
Immunomodulators	Thiopurines (azathioprine,mercaptopurine) and methotrexate	Steroid-dependent disease	Risks: myelosuppression, pancreatitis,malignancies	Moderate, less effective than anti-TNF for endoscopic healing
Anti-TNF therapy	Biologics such as infliximab, adalimumab, certolizumab, pegol	Moderate to severe disease	Severe infections, psoriasis-like skin reactions	High efficacy in inducing and maintaining remission
Alternative Pathways	Vedolizumab (α4ß7 integrin), Ustekinumab (IL-12, IL-23 pathways)	Moderate to severe disease	Limited to gut, newer therapies still under research	Promising, effective in clinical trials
Stem Cell Therapy	Mesenchymal (MSC) and hematopoietic (HSC) stem cells	Severe,refractory disease	Research ongoing, potential immune rejection	Potential for long term mucosal healing and immunological tolerance
Extracellular Vesicles	MSC derived Evs for immune modulation and tissue regeneration	Perianal fistulas, inflammation	Research ongoing, standardization needed	Promising in clinical trials for reducing inflammation and healing

anti-TNF medicine has been found to enhance the effectiveness of perianal fistula closure in the short term. However, this effect does not persist once the therapy is stopped.[44]

Corticosteroids

Budesonide is commonly prescribed to treat moderately localized ileal or ileocecal Crohn's disease due to its lower incidence of side effects compared to prednisone.[44] Systemic corticosteroids have been found to be effective in treating moderate-to-severe Crohn's disease, according to a study conducted by.[44] However, it is not recommended to rely on them for extended periods of time because of the potential health risks associated with prolonged exposure.[46] Attaining remission without relying on steroids is a crucial objective in treatment.[47]

Immunomodulators

Thiopurines (azathioprine and mercaptopurine) and methotrexate can be used as standalone treatments to maintain or achieve remission in individuals with Crohn's disease who rely on steroids. In addition, evidence suggests that these medications can reduce the chances of developing an immune response.[48,49] On the other hand, when compared to anti-TNF drugs, their effectiveness in achieving endoscopic healing is not as high.[50] These medications are frequently linked to low tolerance and are connected to potential risks like myelosuppression, pancreatitis, and an increased likelihood of developing malignancies. Therefore, it is important to be cautious when using them, particularly with young boys and older individuals.[45,48]

Anti-TNF therapy

Studies have demonstrated the high efficacy of anti-TNF medications such as infliximab, adalimumab, and certolizumab pegol in both initiating and sustaining remission in individuals with Crohn's disease.[45,51] Infliximab and adalimumab are commonly prescribed, while certolizumab pegol is not as commonly used.[52] According to a 2004 study by Sands et al., infliximab has proven effective in treating perianal disease. Similarly, adalimumab has been found to enhance fistula repair, as evidenced by the CHARM research conducted by.[53]

These medications have shown effectiveness in treating symptoms that extend beyond the intestines. They can be used to address skin infections, inflammation of the eye, various skin conditions like psoriasis, and a specific type of joint inflammation known as axial spondyloarthropathy.[36] They can offer significant advantages in certain situations, such as in strictures, postoperative prevention, and during pregnancy.[36] When anti-TNFs are combined with immunomodulators, their effectiveness is improved because they become less likely to trigger an immune response.[54]

Cost-effective alternatives with equivalent efficacy and safety have been available in Europe since 2013 and in the USA since 2016.[36] Nevertheless, a notable portion of individuals, approximately 15–20%, may not experience any positive outcomes when using anti-TNFs. In addition, it is worth noting that a certain percentage of

individuals may experience a decline in their response to these medications as time goes on.[51,55] Identifying severe infections and skin reactions resembling psoriasis requires evaluating more recent and safer treatment options.[56,57] It is crucial to thoroughly assess combination therapy's potential advantages and disadvantages, particularly in older individuals who may be more vulnerable to infection and lymphoma.[58]

Alternative pathway therapies for Crohn's disease

Since 2013, biosimilars have been available in Europe and the USA since 2016. These affordable alternatives offer the same effectiveness and safety as their counterparts.[36] However, approximately 15–20% of people may not experience any beneficial results when undergoing treatment with anti-TNFs. In addition, it is worth noting that some individuals may experience a decrease in their responsiveness to these medications over time.[51,55] It's important to consider newer and safer therapeutic approaches when dealing with severe infections and skin responses that resemble psoriasis. Recent studies by Kirchgesner et al.[56] and Xie et al.[57] have shed light on this. It is essential to carefully evaluate combination treatment's potential benefits and drawbacks, especially in older patients more susceptible to infection and lymphoma.[58]

Vedolizumab is designed to target the α4β7 integrin in the gut specifically. It is administered intravenously every 8 weeks, following an initial induction period. The drug's focus on the gut limits its effectiveness in addressing symptoms of Crohn's disease that manifest in areas beyond the intestines.[59] Other medicines that impact the movement of lymphocytes, such as Pembrolizumab and Ontamalimab, have not demonstrated effectiveness in clinical studies.[60,61]

Ustekinumab, a medication that targets specific proteins in the body, is administered through a subcutaneous injection every 8 weeks following an initial intravenous dose based on the patient's weight. In addition, it has been approved for treating plaque psoriasis and psoriatic arthritis.[55] In therapy, exciting progress is made by directing attention toward the IL-12 and IL-23 pathways, particularly on the p19 subunit. This targeted approach is anticipated to improve effectiveness significantly. The phase 3 studies of Risankizumab and the phase 2 trials of Mirikizumab and Guselkumab have demonstrated encouraging results.[41,62–64]

Stem cell therapy for Crohn's disease

Recent breakthroughs in stem cell research and regenerative medicine have shown the potential of using stem cells (SCs) to treat autoimmune disorders. Both mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs) have shown efficacy in treating illnesses such as rheumatoid arthritis, systemic sclerosis, diabetic retinopathy, and glaucoma.[65–67]

Adult progenitor cells, known as mesenchymal stem cells (MSCs), can transform into different types of cells, such as adipogenic, osteogenic, and chondrogenic lineages.[68] Historically, bone marrow (BM) has been widely used as the primary source for MSC production. On the other hand, obtaining MSCs from BM can be quite a complex process, and the donor's age notably impacts the cells' longevity.[69] Wharton's jelly (WJ), a tissue derived from the umbilical cord (UC), is a valuable source for MSCs. Typically discarded at birth, this tissue offers a morally sound and non-intrusive alternative for isolating MSCs.[70] UC-MSCs possess distinct immunological properties, exhibit a remarkable ability to proliferate, and do not raise ethical concerns, rendering them a highly valuable therapeutic resource.[68]

The International Society of Cellular Therapy (ISCT) has set minimum criteria for MSCs. These criteria involve the presence of certain surface markers like CD73, CD90, and CD105 and the lack of expression of CD14, CD34, CD45, CD19, CD11b, CD79a, and human leukocyte antigen-DR (HLA-DR).[69] MSCs can regulate the immune system and demonstrate anti-inflammatory effects. Due to the lack of HLA-DR and costimulatory molecules such as CD80, CD86, and CD40, MSCs can be used in allogeneic and xenogeneic settings.[70]

Various sources can be used to isolate MSCs, such as Wharton's jelly, placenta, bone marrow, dental tissue, adipose tissue, and umbilical cord blood. Due to their convenient isolation, capacity to reduce inflammation, and involvement in immunomodulation, MSCs offer significant potential as a therapeutic option for various autoimmune conditions.[68]

In clinical studies, it has been found that mesenchymal stem cells (MSCs) have the potential to effectively treat perianal fistulas associated with Crohn's disease. These cells are known for their ability to regulate the immune system and have a minimal immune response, making them a promising option for treatment.

Transplanting hematopoietic stem cells (HSC) has proven to be a successful method for restoring immunological tolerance and relieving Crohn's disease (CD) symptoms. Stem cells possess the remarkable capacity to reduce intestinal inflammation, promote lasting restoration of the mucosal lining, and improve the overall well-being of individuals. This makes them a proper choice for treating Crohn's disease.[71] Despite numerous studies supporting the safety and effectiveness of stem cell treatment for CD, there is still ongoing debate surrounding the findings. Thus, it is crucial to carry out additional systematic reviews and meta-analyses to investigate this issue further.

Acellular therapy for CD: extracellular vesicles

Research has shown that extracellular vesicles (EVs) can significantly alleviate the symptoms associated with CD and minimize the risk of complications.[72] Moreover, the promising capabilities of EVs to restore the integrity of cells' protective layer (epithelial barrier function) and balance the population of microorganisms in the digestive system (gut microbiota) hold great potential for advancing the treatment of CD. The potential of delivering bioactive compounds directly to the affected areas makes EVs a highly attractive choice for precise treatment. Scientists are conducting extensive research to study the mechanisms and improve the delivery of extracellular vesicles (EVs) to develop more effective and safer treatments for CD.

Extracellular vesicles (EVs) are minuscule, membrane-enclosed particles that cells secrete. These particles comprise proteins, lipids, and genetic material that can impact the behavior of the cells they contact. Several studies have shown the potential of EVs produced from mesenchymal stem cells (MSCs) to modulate the immune system.[38,73]

Research has shown that vesicles significantly impact immune responses, inflammation reduction, and tissue regeneration. Small structures deliver bioactive chemicals directly to the affected areas in the gastrointestinal system. EVs provide a safer and more closely supervised alternative to live cell treatments, reducing the chances of negative side effects like immune rejection and tumor formation.[73]

EVs derived from MSCs have shown promising results in clinical trials for reducing perianal fistulas in individuals with CD. These studies have shown significant improvements in reducing inflammation and promoting healing of the mucosal lining. These results show that EVs might improve the function of the epithelial barrier and affect the gut microbiota, two important factors in the development of CD.[72]

The effects of extracellular vesicles derived from MSCs on patients suffering from CD-associated perianal fistulas. The study focused on administering MSC-derived extracellular vesicles (EVs) to patients and closely monitoring their progress over a span of several months. The findings revealed a noteworthy decrease in fistula discharge and inflammation, with many individuals observing significant enhancements in the repair of the mucosal lining. This study emphasized the ability of EVs to not only relieve symptoms but also promote long-term healing by enhancing the body's innate healing mechanisms.[74]

In a different study conducted by Wei et al.,[75] researchers investigated the impact of EVs generated from mesenchymal stem cells on intestinal inflammation in individuals with CD. A cohort of individuals diagnosed with CD participated in this study, undergoing a 12-week treatment regimen involving extracellular vesicles derived from MSC. The results showed a significant reduction in indicators of inflammation, such as C-reactive protein (CRP) and fecal calprotectin, commonly used to measure inflammation in people with CD. Furthermore, the endoscopic assessments showed promising results in the healing of the mucosal tissue among the individuals who received treatment, providing further evidence of the effectiveness of EVs.[75]

In addition, Lamb et al.[34] conducted a thorough study that examined multiple clinical studies to evaluate the efficacy of MSC-derived EVs in treating CD. The study examined the results of multiple trials and discovered that EVs derived from MSCs consistently led to decreased inflammation, improved repair of the mucosal lining, and more

favorable outcomes for patients. This extensive study highlighted the promise of EVs as a practical and efficient treatment choice for CD.[34]

These studies provide compelling evidence highlighting the effectiveness of EVs in addressing CD symptoms and enhancing patient outcomes. The clinical studies have shown promising results, demonstrating the potential of MSC-derived EVs to regulate immune responses, decrease inflammation, and support tissue regeneration in individuals diagnosed with CD.

Additional research is required to improve the isolating, characterizing, and delivering EVs to optimize their therapeutic potential. The significance of standardized isolation techniques cannot be emphasized enough. The quality and strength of EV preparations are essential in determining EV-based therapies' success. Thus, it is crucial to implement robust and unwavering isolation protocols.[74,76] The standardization initiatives are vital for ensuring consistent therapy outcomes and facilitating the integration of EV therapies from research settings to clinical applications.[77]

Ultimately, the promising results from research on EVs derived from MSC emphasize the need for further investigation in this field. By conducting extensive research and carefully examining the ways in which EVs offer therapeutic advantages, it becomes feasible to create innovative treatments that significantly enhance the quality of life for people with CD.[72,74,76]

Conclusion

MSC-derived EVs show potential in the treatment of CD. A recent study has indicated that EVs could positively impact immune responses, reducing inflammation and aiding tissue repair. These tiny particles have shown promising results in preventing immune rejection and inhibiting tumor growth, outperforming cells.

Research findings indicate that EVs derived from MSCs have been shown to effectively decrease perianal fistulas and facilitate the healing of CD mucosa. Possible treatments involve using EVs to improve the function of the epithelial barrier and modify the gut microbiota. Drugs based on EVs should be carefully separated and manufactured using established methods to ensure their purity and effectiveness.

Further investigation is necessary to improve EVs' separation, characterization, and delivery. Comprehensive clinical trials are necessary to evaluate medication safety and efficacy and establish universal clinical criteria. Initial studies suggest that EVs could potentially improve patient outcomes by reducing inflammation and promoting the healing of mucosal tissue.

Research on MSC-derived EVs indicates a promising potential for therapy, but more investigation is needed. Thorough research has the potential to result in advancements in treating Crohn's disease, ultimately improving the lives of those affected. Exploring the potential benefits of EVs therapy on CD's treatment and remission effectiveness and safety.[78–86]

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