Stem Cell Therapeutics for Crohn's Disease

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Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC), are a group of chronic, relapsing-remitting, inflammatory conditions of unknown etiology, affecting the gut. The CD is a chronic inflammatory disease of the gastrointestinal tract that might lead to progressive bowel damage and disability. The disease is believed to arise from an uncontrolled immune response against intestinal microbes or microbial components that are transmitted by the intestinal mucosa. According to the most recent data from the CDC, there were over three million adults living with CD or UC in the United States. Approximately 38% and 70% of patients with CD undergo surgery in the first 10 and 20 years after diagnosis, respectively. Current treatments including biologics work by inhibiting inflammatory response but cannot achieve durable remission periods. An effective and safe treatment is urgently required. Stem cell studies and clinical trials have proven the potential to modulate immunity and achieve efficacy in treating CD. This review provides an overview of the regenerative capabilities of stem cells in repairing gut intestinal tissues and promoting immune system regulation in the gut. Additionally, the paper will highlight current limitations and future perspectives of stem cell-related therapy for CD/IBD.

Introduction

Inflammatory Bowel Disease (IBD) includes Crohn's Disease (CD) and Ulcerative Colitis (UC), conditions that are characterized by chronic inflammation of the gastrointestinal tract. CD may affect any part of the GI tract, is patchy in distribution, and has full-thickness inflammation, whereas UC is limited to the colon and rectum, with continuous and superficial inflammation. CD is a debilitating and incurable chronic inflammatory bowel disease (IBD) affecting more than 2.5 million individuals in the Western world and has an increasing incidence in the developing world[1]. CD can affect any part of the gastrointestinal tract. It can progress from initially mild to moderate inflammatory conditions to severe penetrating (fistulization) or stricturing disease. If left untreated, the disease becomes more severe and may also lead to potentially serious complications, including stricture formation, which can lead to intestinal obstructions, anemia, osteoporosis, kidney stones, and colorectal cancer. There is no single treatment that works for everyone, the goal of current medical treatments is to reduce inflammation. With recent advances in molecular biology and understanding of immunologic pathways in IBD, therapies include new biologics and stem cell therapies. Multiple specific drug targets within the inflammatory pathways, via the use of monoclonal antibodies (e.g., Tumor Necrosis Factor α [TNFα], IL-23, IL-17) and, more recently, small molecules (e.g., JAK inhibitors), have been developed[2]. However, inhibiting the inflammatory response (anti-TNF-α antibodies) alone is insufficient to completely cure CD and achieve long-term remission and mucosal healing. Therefore, there is an unmet need for the development of highly effective and safer therapeutics that can advance the management field in CD and provide better clinical, endoscopic, and histologic outcomes.

Stem cells (SCs) have emerged as innovative and effective therapeutics for CD, given their anti-inflammatory and regenerative properties. SCs have the potential to modulate immunity, suppress inflammation, and have anti-apoptotic and pro-angiogenic effects, making them an ideal therapeutic strategy to target chronic inflammation and intestinal damage in IBD[3]. The therapeutic potential of SCs is primarily attributed to their roles in pro-angiogenesis, cellular homing, and immune regulation. Intestinal resident SCs, mainly intestinal stem cells (ISCs) and resident mesenchymal stem cells (MSCs), maintain the structure and function of intestinal structural and immune cells, preserving intestinal mucosal integrity and immune homeostasis. Transplantation of SCs can regulate or rebuild immune cells, repair or supplement structural cells, such as intestinal epithelial cells (IECs), and potentially lead to a complete cure of CD. This review summarizes the current research progress on the safety and efficacy of SC-based therapy for IBD in both preclinical models and clinical trials. We discuss potential mechanisms of SC therapy, including tissue repair, paracrine effects, and the promotion of angiogenesis, immune regulation, and anti-inflammatory effects. The current SC engineering strategies aimed at enhancing the immunosuppressive and regenerative capabilities of SCs for treating intestinal diseases are also highlighted.

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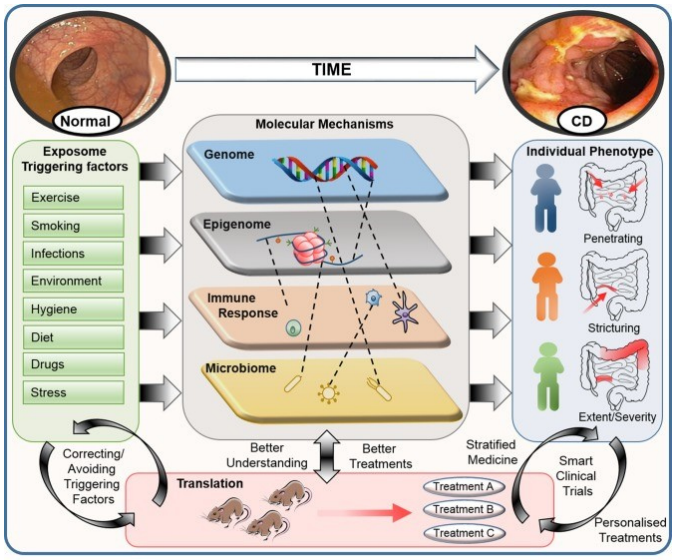

Fig. 1 Crohn's disease (CD): multi-layer interactions in pathogenesis and clinical translation [1]

Results

This review focused on whether SC therapy can improve CD. It is evident after reviewing SC clinical studies conducted so far that SC transplantation reduces gut inflammation and improves the quality of life. However, more high-quality randomized controlled clinical trials and basic research are required.

Discussion

Disease Pathogenesis & Progression

CD pathogenesis involves a complex interplay over time between genetic, epigenetic, immunological, and microbiological mechanisms affected by exposure to triggering factors. Some of the environmental factors are smoking, drug use, diet habits, mental stress, and many other external factors are related to the occurrence of IBDs. Distinguishing features of CD include discontinuous, transmural inflammation involving the whole thickness of the bowel wall, and an inflammatory response associated with lymphoid aggregates and granulomas. The most widely accepted hypothesis purports CD as an immune-mediated condition in genetically susceptible individuals, where disease onset is triggered by environmental factors that perturb the mucosal barrier, alter the healthy balance of the gut microbiota, and abnormally stimulate gut immune responses [1]. In addition, CD has a strong genetic tendency, especially in the first-degree relatives of patients who are at higher risk for IBDs.

The most fundamental pathogenetic pattern of CD/IBDs is the dysregulation of innate and adaptive immunity. CD is mainly characterized by Th1 cell-mediated immune response. CD4+ T cells are involved in CD initiation and development, and Th1 or Th2 cells are involved in inflammation [4]. The levels of mucosal CD4+ T helper (Th) cells that secrete effector cytokines such as TNF-α and IFN-γ are abnormally high in the guts of CD patients. In response to different types of pathologic factors and inflammatory cytokines, naive CD4+ T cells can differentiate into distinct subsets of CD4+ Th cells, such as Th1, Th2, Th17, and CD4+FoxP3+ T regulatory cells (Tregs). Th1 and Th17 cells can secrete a variety of inflammatory cytokines that trigger the infiltration of inflammatory cells into the intestinal epithelium, leading to acute or chronic enteritis. In the CD mucosa, macrophage-derived IL-12, IL-18, and TNF-α are overexpressed, driving the Th1 immune response to increase the production of IL-2 and IFN-. This response is thought to cause intestinal inflammation [5]. Th17 cells are induced by IL-6 and TGF-β and produce IL-17A, IL-21, and IL-22, and those soluble factors will cause inflammation in CD mucosa. Also, deficiency or aberrant activation of intestinal MSCs may lead to disturbance in mucosal and immune homeostasis, thus contributing to the pathogenesis of IBD.

CD progression can vary from patient to patient, but the most common progression starts with moderate inflammation and then advances to more severe forms of inflammation such as a stricturing disease. Early-stage CD is often characterized by mucosal inflammation compared to advanced stages involving transmural inflammation. This can lead to injuries such as fistulas, strictures, and abscesses. The disease's erratic nature is a hallmark of CD, complicating diagnosis and treatment. Over time, chronic inflammation can cause irreversible tissue damage, raising the risk of colorectal cancer and other serious complications. The course of CD is very erratic and unique with periods of both relapse and continued remission. Some factors that may influence the disease progression include environmental triggers, changes in diet, and the patient's immune response. Thoroughly understanding the clinical progression of CD is vital to developing new and improved therapies that may be able to stop or even reverse the damage caused by CD. Stem cell treatment, immunomodulatory treatment, and biologics are steppingstones to finding the ultimate therapy for CD

Stem Cells

Stem cells are undifferentiated cells that can differentiate into specific cells of tissues or organs. SC therapy is a novel therapeutic approach in immune-mediated conditions, and, because of their peculiar biological properties, stem cells represent a promising tool for regenerative medicine and chronic inflammatory diseases [6]. The goal of stem cell-based therapy is to rejuvenate or replace dysfunctional tissues and organs through stem cell pluripotency, self-renewal, and regenerative cytokine secretion. As expectations rise for regenerative treatment

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through the application of stem cell therapies, the number of applications of various types and stem cell sources has increased, and stem cell therapies have diversified from autologous (isolated from the same individual, i.e. the patient himself) to allogenic (isolated from a donor, ideally human leukocyte antigen [HLA]-matched) to induced pluripotent stem cells (iPSCs))[7]. The SC treatments can vary in risk, depending on the cell manufacturing process and clinical experience and among other factors, the strengths and weaknesses of each type of stem cell should be identified in order to determine the maximum therapeutic effect of stem cells in various diseases. As stem cells derived from various sources have different characteristics, capabilities, potential, and efficiency, selecting the right source of stem cells that is appropriate for the target can be effective in assuring treatment efficiency[7]. Key characteristics and differences of various stem cells with an emphasis on therapeutic treatments for CD is summarized below.

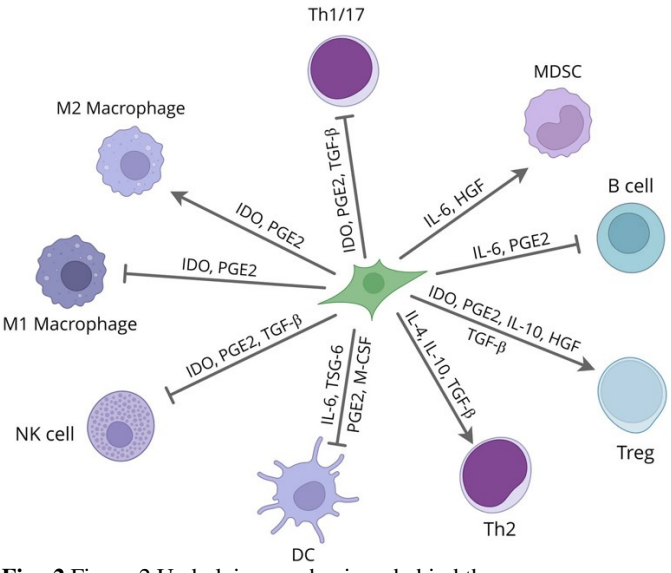

Fig. 2 Figure 2 Underlying mechanisms behind the immunomodulatory attributes of MSCs[8]

Stem Cells and CD

The use of stem cells in CD/IBD treatment is expected to achieve sustained remission and mucosal healing. Preclinical studies in IBD models are increasing, and various types of stem cells, such as embryonic stem cells (ESCs), MSCs, hematopoietic stem cells (HSCs), ISCs, and iPSCs, have demonstrated positive efficacy and stable safety in IBD animal models. These cells have the potential to directly improve chronic inflammation in the intestine by modulating immune cells and repairing the intestinal mucosal barrier. In addition to addressing inflammation, they can play a beneficial role in enhancing intestinal microecology, resolving microcirculation disorders, and preventing fibrosis and cancerization, among other benefits. The CD is usually described as a Th1/17-associated disorder since the main inflammatory cytokines in this condition are the Th1/17-related molecules like IL-12, IL-17, IFN-γ, and TNF-α[8]. The gastrointestinal tract is protected from adverse substances in the gut environment by a single layer of epithelial cells that are known to have great regenerative ability in response to injuries and normal cell turnover. The gastrointestinal tract is highly vulnerable to damage, tissue inflammation and diseases once the degradation of the mucosal lining layer occurs. In recent years, HSCs and adult MSCs have shown efficacy in treating IBD. In addition, numerous clinical trials have evaluated the efficiency of MSCs in treating the disease.

Inflammation and Immune Suppression Properties of Stem Cells

Inflammation is generally present in damaged tissues, without which the initiation and completion of the repair process cannot occur. However, excessive inflammation impairs tissue regeneration. MSCs also modulate the cytokine milieu generated by different T cell subsets by decreasing the pro-inflammatory cytokine production and increasing the anti-inflammatory cytokine production. Some cytokines like IFN-γ, TNF-α, and IL-17 are usually reported to be downregulated and L-10, IL-4 upregulated, thereby indicating a possible MSC-mediated alternation in Th1/Th2/Th17 subset balance[9]. MSCs mediate their immunomodulation via the release of soluble factors or by cell-cell contact manner (Figure 2). Some key soluble factors are: transforming growth factor (TGF)-β, hepatocyte growth factor (HGF), IL-6, indolamine dioxygenase (IDO), prostaglandin E2 (PGE2), human leukocyte antigen (HLA)-G5, TNF-stimulated gene-6 (TSG-6), IL-1 receptor antagonist (IL-1Ra) and IL-10. IDO causes reduced proliferation and cytotoxicity of natural killer (NK) cells and decreases the Th17 differentiation with induction of Tregs.

Higher levels of pro-inflammatory factors, such as IL-1β, IFN-γ, and TNF-α, stimulate MSCs to reduce inflammation and avoid autoimmune reactions by releasing, for example, TGF-β, IL-10, IDO resulting in an inhibition of the migration, maturation, and antigen presentation of dendritic cells (DC), and of T-cell function and proliferation, along with the proliferation of Tregs. Therefore, the TGF-β, IL-10, and IDO levels have been proposed as the switcher between the pro- and anti-inflammatory effects of MSCs[10].

Mucosal Healing and Regeneration Properties of Stem Cells

The intestinal barrier makes a separation between the body and the contents of the intestine. It consists of various sections, including a mucus layer comprising antibacterial peptides lining the luminal surface of the epithelium, the

Table 1. The properties of different stem cells with an emphasis on therapeutic treatments for CD cell therapies.

Stem Cells	Classification	Preclinical/Clinical Use?	Advantages	Disadvantages
MSCs	Multipotent	Clinical	• Potent immunomodulatory and anti-inflammatory	• Adverse immune reactions
			• Repair damaged tissues	• Tumor formation
			• Tumor homing	• Transmit viral infections and are vulnerable to many microorganisms
			• Attenuate immune responses	• More affected by donor age
				• A limited number of cells
BM-MSCs	Multipotent	Clinical	• Immune regulation and immunosuppression	• Require younger donors
			• Ease of extraction and culturing	• Invasive harvesting procedure
			• Bone and cartilage reparatory cells	• Differentiation potential of BM-MSCs decrease with aging
			• Support angiogenesis	
			• Autologous BM-MSCs are used for such regenerative therapies	
			• Lower risk immune rejection	
			• Increased anti-inflammatory expression	
			• Homing features	
ESCs	Pluripotent	Preclinical	• Detter differentiation potential	• Derived from human embryos leading to ethical and FDA concerns
			• Longer lasting proliferation capacity	• Tumorigenic potential
			• Immune-privilege and immunomodulatory in transplantation as allogeneic cells	• Difficulty in vitro work
			• A high degree of inherent plasticity, which assists in the adoption of ESCs by the recipient tissue	• Difficulty in controlling differentiation
HSCs	Multipotent	Clinical	• Better differentiation potential	• Sensitive to inflammation
			• Ultimate source of blood and immune cells	• Extensive inflammation may cause HSC exhaustion/ senescence and malignant transformation
			• Responsible for the generation of all the lineages of the blood	• Long-term exposure to inflammation can impair HSC self-renewal activity and accelerate aging
hUC-MSC	Multipotent	Clinical	• Control inflammatory response	• Uncontrollable immune regulation
			• Promote granulation angiogenesis	• Abnormal accumulation
			• Inhibit scar formation	• Nontherapeutic differentiation
			• Derived from discarded umbilical cord tissue, with the advantages of easy obtaining	• Low survival of transplanted cells
			• Immunomodulatory, and anti-inflammatory properties	
			• Stronger proliferation, differentiation, and immune regulation abilities	
ISCs	Pluripotent	Clinical	• Differentiate into the mature cell types required for normal gut function	• Fixed differentiation lineages
			• High self-renewal rate as well as remarkable regenerative properties	• High Heterogeneity
			• ISCs are a valuable cell source to grow organoids	• high manufacturing costs, limited scalability, and risk of pathogen contamination
			• ISCs/Intestinal organoids are human-derived and nearly physiological, and can simulate multiple types of organ-specific disease states in vitro	• Low reproducibility
IPSCs	Pluripotent	Clinical	• Not derived from human embryos	• Production of iPSCs using retroviruses is associated with cancer
			• Creation of cell lines that are genetically tailored to a specific patient eliminating immune rejection	• Retroviruses can insert DNA anywhere within a cell's genome, allowing for potential activation of cancer-causing oncogenes
			• Reverse injury or disease	• C-Myc, which is one of the genes commonly used in iPSC reprogramming, is a known oncogene whose over-expression could also cause cancer
pESCs	Totipotent	Preclinical	• Allogeneic	• Loss of heterozygosity
			• Immunomatching	• abnormal imprinting and high levels of homozygosity may complicate applications of pESCs
			• Less tumorigenic	
ADSCs	Multipotent	Clinical	• Participate in immune regulation	• May increase the risk of tumor growth and metastasis
			• Inhibit of scar formation	• Uncertainty about the clinical efficacy of ADSC-based therapies
			• Rich source	
			• Regulate metabolism and the immune system	
			• Easy accessibility	

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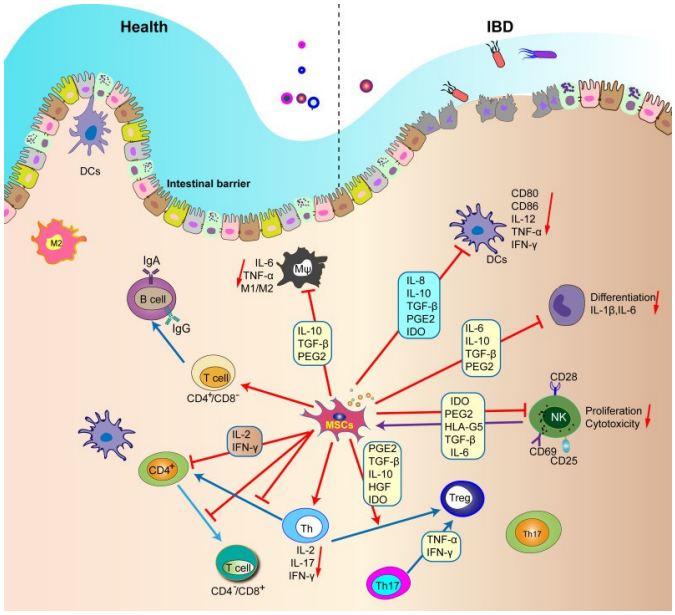

Fig. 3 Gastrointestinal Trac - MSC can secrete PEG2, IL-10, TGF-β, inducible, IDO and IL-6 to inhibit the proliferation of T cells and NK cells, thus reduce the production of inflammatory cytokines in Th1 and Th17, and inhibit immune response and inflammation[t1]

epithelial cell monolayer, junctional proteins, intraepithelial lymphocytes (IELs), and also a subepithelial layer of extracellular matrix (ECM) and mesenchymal cells like myofibroblasts and fibroblasts (Figure 3). The intestinal barrier provides a shield versus potentially damaging molecules and also pathogenic bacteria, thus supporting intestine immune homeostasis. Mucosal healing is associated with a more favorable prognosis for patients with IBD, including lower relapse and hospitalization rates, as well as a diminished risk for surgery.

In CD, evidence points to a dysfunctional epithelium (innate and acquired) as a pathogenic factor leading to a breakdown in gut homeostasis and loss of barrier function[2]. In addition, specific damage to the ISCs results in further de-regulation and the loss of the capacity to regenerate a functional epithelium with a full complement differentiated cells. More importantly, there is accumulating evidence to show that ISC function is affected in IBD/CD. In human CD, a reduction in the ISC population is observed within active disease compared with nonaffected gut mucosa. This is shown by correlating pathological assessment of activity with ISC frequency using in situ hybridization of the LGR5 stem cell marker[11]. The perturbation of ISC function or potential may contribute to failure of IBD mucosa to heal or return to normal homeostasis. It is of interest that a low ISC population appears to predict future clinical recurrence in CD. The gastrointestinal tract is lined by a single layer of columnar intestinal epithelial cells—a sophisticated multifaceted barrier that comprises several specialized cell types, each with a distinct function. Intestinal epithelial cells (IECs) play a critical role in maintaining the barrier's integrity given their anatomical and functional location. MSCs promote the expression of TJs proteins in IECs, thereby reducing inflammation-stimulated permeability. In addition,[12] revealed that induced pluripotent stem cells (iPSC)-derived MSCs could boost IECs proliferation to ameliorate mucosal healing in a mice colitis model by TSG-6 secretion. In vitro, TSG-6 could promote Akt phosphorylation in mice colonoids (primary cultures derived from intestinal crypts), reflecting the key role of Akt activation in the TSG-6-mediated proliferation of IECs. Similarly, administration of iPSC-MSCs promoted IECs proliferation, raised the Lgr5+ISCs frequencies, and potentiated intestinal angiogenesis in colitis rodents. Positive regulation of Lgr5+ISCs proliferation and differentiation, as shown by exogenous PGE2 injection, may augment intestinal integrity and promote mucosal healing in IBD patients[8]. Thus, these early studies provide the premise for an intervention that is targeted toward the correction of ISCs in the IBD gut (either by replacement with healthy ISCs or, augmentation, or restoration of ISC function).

Overview of SCs for IBD Treatment

Mesenchymal Stem Cells (MSCs)

Human mesenchymal stem cells (MSCs), also known as mesenchymal stromal cells or medicinal signaling cells, are important adult stem cells for regenerative medicine, largely due to their regenerative characteristics such as self-renewal, secretion of trophic factors, and the capability of inducing mesenchymal cell lineages. MSCs also possess homing and trophic properties modulating immune system, influencing the microenvironment around damaged tissues and enhancing tissue repair, thus offering a broad perspective in cell-based therapies[13]. MSCs secrete bioactive factors that favor tissue remodeling and repair, as well as immunoregulatory properties. MSCs are present in the umbilical cord blood, placenta, muscle, and other tissues, with bone marrow and adipose tissue being the most important sources[14]. Recent studies have also implicated the importance of intestinal MSCs in digestive organ development, mucosal tissue, and immune homeostasis, which can provide multiple niche signals to support functional integration of mucosal epithelial cells, immune cells, and gut microbiota[5]. Most recently, the emerging studies using scRNA-seq have significantly improved our understanding of the heterogeneity and the distinct role of diverse subsets of intestinal MSCs in regulating mucosal homeostasis and immunity by providing different niche signals under both physiological and inflammatory conditions. For instance, recently identified distinct subpopulations of stromal fibroblasts with gene signatures that are differentially regulated

by chronic inflammation through scRNA-seq analysis of colon-derived mesenchymal stromal cells provide mechanistic insight into how inflammation affects the function and behavior of intestinal MSCs and their crucial role in orchestrating mucosal tissue remodeling and healing. Besides MSCs, cytokines and extracellular vehicles (EVs) which are released by MSC also have the therapeutic effect on CD. Because of the low immunogenic profile, which decreases the potential for cell rejection and graft-versus-host-disease, more and more studies begin to focus on the paracrine action of MSC. MSC secrete growth factors, exosomes, cytokines, and metabolites that inhibit inflammation, restore the intestinal mucosal barrier, and are protective. MSCs regulate immune responses by releasing various modulatory factors including PGE2, IL-6, TSG-6, and IDO. The constant interaction between MSCs and the immune system is key to balancing inflammatory responses and maintaining tissue homeostasis. There is increasing evidence that MSCs play an important role in both innate and adaptive immunity. For instance, MSCs can inhibit CD4+ (helper) and CD8+ (cytotoxic) T cell, affect B cell functions through cell-to-cell contact, suppress the proliferation and cytotoxicity of NK cells, as well as increase Tregs generation via cell communication and soluble factors both in vitro and in vivo [13]. MSCs transplantation also decreased expression of IL-6, TNF-α, and IFN-γ and concurrently increased the levels of IL-10, TGF-β, and forkhead box protein P3 (Foxp3), a crucial regulator of Tregs, in colon tissues. MSCs could decrease CD4+T cell proliferation, inhibit Th1/Th17 cells activation, while inducing Th2 cell's function. These events finally diminish pro-inflammatory IL-17 and IFN-γ, and improve TGF-β, IL-10 levels in colon tissue of MSCs-treated IBD models. Regardless of the pro-inflammatory cytokines, systemic administration of MSCs could affect T-box expressed in T cells (T-bet) and retinoid-related orphan receptor gamma(t) (RORγt) expression in T cells. T-bet and RORγt, as a central regulator of Th1 and Th17 cells, respectively, act as causative factors in IBD progress. Thus, their inhibition by MSCs-secreted mediators could lead to the suppression of Th1/Th17-related pathological events in IBD patients [8]. An increasing number of studies show that many of the therapeutic effects of MSCs may be the result of the paracrine factors secretion of EVs, rather than cellular engraftment and response to the site of injury [15]. MSC-EVs cannot self-replicate, thereby becoming attractive cell-free and safer therapeutic sources because uncontrolled cell division and risks of contamination with other cells are prevented. Moreover, allogenic MSCs have good safety profiles for patients with inflammatory bowel disease for up to 1 year. [2]

BM-MSCs

Bone marrow-derived mesenchymal stem cells (BM-MSCs) are a potential treatment for CD. Studies have demonstrated that local administration of autologous or allogeneic BM-MSCs achieved obvious clinical efficacy in patients with fistulizing CD by downregulating local immune responses and initiating wound healing. BM-MSCs can restore intestinal epithelial cell by differentiating into epithelial cells through "cell fusion" in vitro under certain culture conditions that include HGF, EGF, KGF, and IGF-II. BM-MSCs were involved in the repair of intestinal epithelial cell injury through the cell fusion mechanism after transplantation [5]. BM-MSCs have been shown to reverse the epithelial-mesenchymal transition (EMT) of TGF-β1-treated IEC-6 cells by carrying miR-200b, resulting in a significant reversal of intestinal fibrosis. Trials using bm-MSC were also performed in CD complicated by complex perianal fistula. Local administration of autologous BM-MSC was well tolerated and feasible in a study involving 10 patients with CD and actively draining complex perianal (n=9) and enterocutaneous (n=1) fistulas. Local injections were scheduled at 4-week intervals; all patients showed either complete (n=7) or partial (n=3) fistula closure at 1 year, with no adverse effects. All patients improved their disease activity, especially after the second administration. Endoscopic healing was also observed in 7 out of 9 patients with perianal disease and endoscopic rectal activity. However, in the long-term follow-up, the probability of fistula relapse-free survival decreased over time was 88% at 1 year, 50% at 2 years, and 37% during the following 4 years [16].

Hematopoietic Stem Cells (HSCs)

Hematopoietic stem cells (HSCs) may be used in autologous or allogeneic transplantations for the treatment of patients with diverse hematopoietic disorders and several inherited immune-deficient and autoimmune diseases and to reconstitute the hematopoietic cell lineages and immune system defense. Use of hematopoietic stem cells transplantation (HSCT) in IBD is restricted to severe CD with few therapeutic options. These are patients who do not respond to standard treatment in whom surgery is not an option due to extent of disease. The first phase I trial using autologous HCST was conducted in Chicago and recruited 12 patients with active moderate to severe CD refractory to conventional therapies. Eleven of 12 patients demonstrated sustained remission after a median follow-up of 18.5 months, and one patient developed recurrence of active CD [17]. The rates of clinical remission induced by HSCT seem to be the highest ever reported in CD, when compared to steroids or any biological agent, even in the difficult clinical scenario of refractory disease. In some reports, objective deep remission has been reported, in terms of not only clinical but also endoscopic response, in higher percentages than any conventional treatment. However, some impressive long-term remissions, maintained continuously for more than 10 years without any other treatment, suggest the need to better understand the mechanisms of action of HSCT and, therefore,

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to better select the best responders among CD patients and how to protect them from disease relapse. As stated in the EBMT guidelines, autologous HSCT should be considered as a therapeutic option at second line or beyond for patients with severe autoimmune diseases progressing despite standard established and/or approved therapy [16].

Human Umbilical Cord -Mesenchymal Stem Cells (hUC-MSCs)

hUC-MSCs are intended to treat multiple immune diseases (for instance, psoriasis, liver failure, and lupus nephritis) by intravenous infusion. Compared with human bone marrow and adipose-derived mesenchymal stem cells, they are easier to obtain, have demonstrated strong proliferation and differentiation capability and strong plasticity, with less ethical controversy and have less cell loss after cryopreservation [18]. In a recent study on a TNBS-induced colitis mice model, hUC-MSCs transplantation protected against experimental colitis by promoting CD5+B cells and IL-10-secreting CD5+regulatory B cells (Bregs). It has previously been evinced that deficiency or reduction of Bregs function intensifies intestinal inflammation in mice models and is in association with CD/IBD pathogenesis. In addition to the enhanced Bregs population, hUC-MSCs therapy led to improved Tregs while decreasing Th1/Th17 cell populations in colon tissue of treated mice [8].

Embryonic Stem Cells (ESCs)

ESCs are pluripotent cells derived from the inner cell mass of blastocytes and have the potential to induce cell types of all three-germ layers. ESCs have established cell lines that can be maintained through in vitro culture. They are pluripotent cells that can be differentiated into almost any type of cell present in the body. In a study aimed to evaluate the differentiation and repair potential of murine ESCs in a murine model of CD, histopathological analysis showed improved colon tissue and immune studies indicated a shift from TH1 to TH2 response, suggesting immune recovery. Overall, the findings suggest that the differentiation and repair capabilities of embryonic stem cells could offer new therapeutic options for treating and preventing inflammatory bowel disease [19].

However, the use of ESCs in clinical practice has a major limitation related to ethical concerns as the generation of ESCs is linked to the use of germ cells and destruction of human embryos.

Intestinal Stem Cells (ISCs)

Mucosal healing is associated with a more favorable prognosis for patients with CD, including lower relapse and hospitalization rates, as well as a diminished risk for surgery. Successful transplantation of intestinal stem cells (ISCs), which are responsible for tissue homeostasis and injury response in murine models of experimental colitis demonstrated that they adhere to and become an integrated part of the epithelium, thereby improving mucosal healing. Hence, ISC transplantation might constitute an appealing therapeutic approach to re-establish the epithelial barrier in CD/IBD. However, if the patient's ISC cells were to contain genetic mutations that predispose to malignancy, then transplantation might lead to risk of malignant transformation in a greater area of the intestine after engraftment. ISCs are located at the base of the intestinal crypts where they renew the epithelium through differentiation to multiple epithelial progenies and drive mucosal regeneration. ISCs can be cultured in vitro, giving rise to three-dimensional self-organizing structures called organoids. Intestinal organoid is a three-dimensional organlike structure grown in vitro, consisting of intestinal epithelial cells. The nomenclature varies and is also referred to as a mini gut. In studies investigating organoid therapy to restore the epithelial barrier function, the engrafted organoids successfully healed areas of epithelium and retained a human phenotype both in terms of shape and size of villi. In a model more representative of IBD, after exposure to DSS colitis, organoid transplant recipient mice were found to have areas of healed mucosa, with a full complement of differentiated cell types [2].

Induced Pluripotent Stem Cells (iPSCs)

iPSCs are artificially created stem cells. These cells are made by reprogramming adult somatic cells such as fibroblast cells. They share many of the characteristics of ESCs, including self-renewability, pluripotent differentiation, and malformed species performance. Unfortunately, these cells have little scientific evidence regarding changes in cell-specific regulatory pathways, gene expression, and epigenetic regulation. In murine models of IBD, transplantation of iPSC-derived intestinal cells led to significant histological improvements, including reduced inflammation and tissue damage [20]. In a separate study on mouse models of IBD, the regenerative effects of iPSC-MSCs were explored and the mechanisms by which iPSC-MSCs promote mucosal healing via tumor necrosis factor-α-stimulated gene 6 (TSG-6) [12]. The iPSC-MSC treatment promoted mucosal healing in colitis mice, accompanied by increased epithelial cell proliferation, CD44-positive cells, and Lgr5-positive cells. Organoids co-cultured with iPSC-MSCs showed increased epithelial cell proliferation, CD44-positive cells, and Lgr5-positive cells, which was abolished by TSG-6 knockdown. The study concluded that iPSC-MSCs promoted epithelial cell proliferation to accelerate mucosal healing in a murine colitis model via TSG-6 through hyaluronan–CD44 interactions in an Akt-dependent manner, demonstrating a patient-specific "off-the-shelf" format for IBD/CD treatment. However, the use of iPSCs for cell therapy also has concerns and challenges.

The potential of tumorigenicity caused by the non-complete differentiation, accumulation of genetic mutations, epigenetic abnormalities, and expression of the reprogramming factors are considered as the major challenges.

Adipose Derived Stem Cells (ADSCs)

ADSCs appear to be the most advantageous cell type for regenerative therapies owing to their easy accessibility, multipotency, and active paracrine activity. The great advantage of ADSCs is that they can be harvested through a less invasive method and in larger quantities without any ethical concerns. ADSCs repopulate damaged tissues via adhesion, proliferation, and differentiation. ADSCs have paracrine activity and secrete a broad spectrum of bioactive molecules, such as cytokines, antioxidant factors, chemokines, and growth factors. ADSCs have stronger proliferation ability and immunomodulatory function compared with BM-MSCs. ADSCs can suppress dendritic cell differentiation, immunoglobulin synthesis, CD8+ and CD4+ T lymphocytes , natural killer cell proliferation and promote M2 macrophage polarization and Treg proliferation. ADSCs can alleviate excessive inflammation and regulate the immune system through direct cell–cell contact or indirect paracrine activity. ADSC-exo-based treatment can reproduce ADSCs' immunomodulatory function and overcome the limitations of traditional cell therapy. The data referring to the clinical efficacy of AD-MSC transplantation in the treatment of complex perianal fistulas in CD are also promising and darvadstrocel (allogeneic AD-MSCs) has recently become commercially available in Europe in adult patients with non-active/mildly active luminal CD, when fistulas have shown an inadequate response to 1 conventional or biologic therapy [16].

ADSCs can be recruited to tumors and integrated into the tumor stroma, after which some ADSCs are converted to cancer-associated fibroblasts, while others remain as ADSCs [21]. Meanwhile, undifferentiated ADSCs in tumors exhibit active paracrine activity and secrete various cytokines that facilitate tissue regeneration, including growth factors and VEGF [14]. These bioactive molecules secreted into the tumor microenvironment may enhance tumor vascularization, promote the survival and proliferation of tumor cells, and accelerate tumor progression.

MSC Mechanisms Summary

MSCs possess biological and regenerative effects mostly due to their secreted trophic (regenerative) factors that mediate cell-to-cell communications, regulate cell proliferation/differentiation, and have anti-inflammatory properties. By producing extracellular vesicles (EVs), cytokines, and growth factors, MSCs have demonstrated excellent potential to modulate both adaptive and innate immune system responses. These findings are supported by in vitro, and in vivo experiments, as well as by clinical data that shows a complex network of interactions between immune cells and MSCs [13]. The immune modulating functions of MSCs are via secreted paracrine factors such as the beta fibroblast growth factor (bFGF), the insulin-like growth factor 1 (IGF-1), the vascular endothelial growth factor (VEGF), the epidermal growth factor (EGF), the tissue inhibitor of metalloproteinase-1 (TIMP-1), progranulin, and the brain-derived neurotrophic factor (BDNF), or by direct cell-to-cell communications with various immune cells such as T cells, B cells, natural killer (NK) cells, macrophages, monocytes, dendritic cells (DCs), and neutrophils, stimulating or suppressing the immune responses.

Stem Cell Delivery

Dosage, dose frequency, intervals, and suspensions are important parameters for MSC administration. The dosages reported in many clinical trials are heterogeneous depending on the route of injections. The MSC dosages are usually decided by the patient's condition and therapeutic properties. In MSC clinical trials, dose frequency, interval, and dosage vary significantly. The dosages are typically described in cells/kg body weight (0.5–12×106 cells/kg as a single dose). Allogeneic MSCs doses might go up to 1×10^8 [13]. In conclusion, it is essential to evaluate in preclinical studies and thoroughly evaluate the condition of patients, progression of diseases, treatment regimens, and the potential route risks before choosing the optimal MSC transplantation dose and administration method.

Methods

Stem Cell Studies for CD/IBD Treatment

The International Society for Cellular Therapy (ISCT) established unique criteria that apply for all MSCs isolated from different sources. Based on the ISCT criteria for MSCs, authentic human MSC-like cells must express certain MSC positive surface markers 5-nucleotidase (CD73), Thy-1 (CD90), and Endoglin (CD105) and they must lack the expression of macrophage marker CD14, HSC marker CD34, lymphocyte marker CD45, B cell marker CD19, B-cell antigen receptor complex-associated protein alpha chain CD79a and MHC class II cell surface receptor HLA-DR [13]. Clinical trials based on MSCs therapy in IBD conditions registered on https://clinicaltrials.gov (June 2022) were demonstrated in Figure 4. The promising results from animal studies have encouraged researchers to design and conduct a variety of clinical trials. Meanwhile, both autologous and allogeneic MSCs transplantation have been accomplished given their immune-suppressive and regenerative competencies with remarkable

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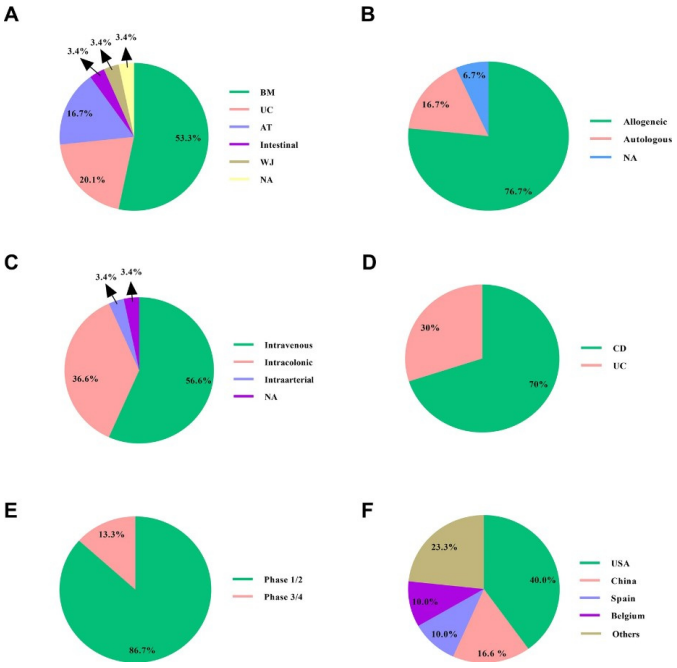

Fig. 4 -MSCs therapy-based clinical trials in IBD conditions registered on https://clinicaltrials.gov (June 2022). The schematics illustrate clinical studies based on cell source (A), cell type (B), administration route (C), condition (D), study phase (E), and study location (F). Inflammatory bowel diseases (IBD), mesenchymal stem/stromal cell (MSC), bone marrow (BM), umbilical cord (UC), adipose tissue (AT), Wharton's jelly (WJ), Crohn's disease (CD), ulcerative colitis (UC), not applicable (NA).

safety and acceptable efficacy.

Autologous Studies

Recent studies involving autologous stem cell treatments for Crohn's disease have shown promising results. In one trial, five patients with refractory Crohn's fistulas received intracolonic administration of autologous AT-MSCs at a dose of 35 *times*10^6 cells per patient. This treatment had no severe side effects and led to the complete cessation of drainage in three of the patients over a six-week follow-up period[22]. Another phase 1 trial with twelve patients demonstrated that intracolonic administration of AT-MSCs was both safe and effective, with complete fistula healing achieved in 57% of the patients[23]. The primary adverse effect observed was proctalgia, which lasted a few days; additionally, two patients developed small abscesses, one experienced urinary retention, and another had minor bleeding during liposuction. A different phase 1 trial showed that injecting 1–2×107 cells of AT-MSCs per patient was safe and feasible in Crohn's disease patients[24]. Autologous BM-MSCs administered intravenously at a dose of 1–2×106 cells/kg also did not cause serious side effects in ten patients with refractory Crohn's fistulas[25]. This intervention led to a reduction in the Disease Activity Index (DAI) in three patients over six weeks, although three others required surgery due to disease worsening. Additionally, another study reported that systemic injection of autologous BM-MSCs at a dose of 1×10^7 cells/kg was modestly safe and feasible in twelve patients with Crohn's disease[26].

Allogeneic Studies

A trial involving 82 patients, with 41 in each control and intervention group, demonstrated that systemic injection of allogeneic UC-MSCs at a dose of 1×10^6 cells/kg could reduce the DAI, Harvey–Bradshaw Index (HBI), and corticosteroid dosage without causing serious side effects[27]. Additionally, local administration of 3×10^7 allogeneic MSCs/ patient improved the healing of perianal fistulas[28]. Intracolonic injections of $3 - 9 \times 10^7$ allogeneic BM-MSCs /patient resulted in smaller fistula tracts after four years, with no long-term side effects observed in CD patients[29]. In a phase 1/2 clinical trial, local administration of allogeneic AT-MSCs at a dose of 20×10^6 cells/patient in 24 CD patients led to a reduction in the number of draining fistulas for 69.2% of patients, complete closure of the treated fistula in 56.3% of patients, and closure of all existing fistula tracts in 30% of patients[30]. These results indicated the safety, feasibility, and efficacy of allogeneic AT-MSCs in treating CD. Forbes and colleagues conducted a phase 2 trial, showing that weekly transplantation of 2×10^6 allogeneic MSCs/kilogram for four weeks reduced both DAI and the Crohn's Disease Endoscopic Index of Severity (CDEIS) scores in patients with luminal CD who were refractory to biologic therapy[31]. Furthermore, a phase 3 randomized, double-blind controlled trial, conducted across 49 hospitals in eight countries from July 6, 2012, to July 27, 2015, evaluated the safety and efficacy of local administration of expanded allogeneic AT-MSCs (Cx601)[32]. Intralesional injection of 120×10^6 Cx601 cells per patient in 107 CD patients demonstrated an acceptable safety profile and significant efficacy, particularly in those who did not respond to conventional or biological treatments. MSC therapy was well tolerated, and clinical remission post-treatment was sustained for up to 104 weeks in patients with perianal fistulizing CD[33]. According to researcher-initiated registered data from the US National Institutes of Health, there has been a rapid development of cellular therapy during the last decade using MSCs in clinical trials. The number of MSC-based clinical trials has doubled over the last five years. As of July 14th, 2021, 1014 MSCs-based clinical trials have been registered in the ClinicalTrials.gov database either as completed or in process. Also, there is a double-blind study (NCT01541579) conducted at nearly 50 hospitals in Europe and Israel, which investigated the treatment of 212 CD and perianal fistula patients with allogeneic AD-MSCs (Cx601)[32]. After one year, the follow-up study showed that Cx601 was safe and effective compared to a placebo. The trial enrolled patients with CD who had complex

perianal fistulas that had not adequately responded to standard treatments. Cx601 treatment led to a significantly higher rate of complete closure of perianal fistulas compared to the placebo group. The study concluded that expanded allogeneic AD-MSCs are a safe and effective treatment for complex perianal fistulas in CD.

Future Perspectives of Stem Cell-Based CD Therapies

Pre-treated (Primed) MSCs

AD-MSCs induced with IFN-γ and kynurenic acid substantially upregulated the expression and secretion of IDO-1, finally alleviating CD pathology-like colitis injury and fibrosis in vivo. Likewise, systemic injection of MSCs upon exposure with IL-25 decreased infiltrating inflammatory cell frequencies and enhanced Tregs in serum and colonic mucosa of the IBD rat model, leading to inhibited intestinal inflammation and decreased DAI score. In addition, animal models exhibited that IFN-γ increases the efficacy of human UCB-MSCs transplantation by improving PGE2 release and IDO activity[8]. PGE2 in association with IDO inhibits Th1 cell differentiation and enhances Tregs differentiation, suggesting that a combination of PGE2 and IDO may be effective therapeutic mediators for potentiating the MSCs-induced immunosuppression.

Gaps:

- In particular, knowledge is limited with respect to the downstream pathways of IDO-1 and PGE2 in mitigating inflammation and fibrosis.
- The specific interactions between MSC-secreted factors and Tregs, such as IDO and PGE2, are not fully defined

Key Questions:

- How do IDO-1 and PGE2 interact in modulating Treg activity and suppression of inflammation in CD?
- Which are the best priming agents or combinations thereof, such as IFN-γ, kynurenic acid, IL-25 for different stages of CD?

Genetically Modified MSCs

Current reports exhibit that overexpression of various genes such as intercellular adhesion molecule (ICAM), CXCR4, and CXCR2 can improve MSCs homing to the injured area and thus enhance succeeding anti-inflammatory and pro-survival effects in IBD animal models. ICAM-1 overexpressing MSCs also reduced Th1 and Th17 subpopulation while enhancing Tregs frequency in the spleen of treated mice, ensuring down-regulated IFN-γ and IL-17A and upregulated Foxp3 levels. Other studies have focused on enriching the antioxidant potential of MSCs using genetic engineering. Nuclear factor erythroid 2-related factor (Nrf2) signaling adjusts multiple gene expressions by making interfaces with the antioxidant response element (ARE). Up-regulation of the Nrf2/ARE axis dampens numerous pathologic mechanisms correlating with the autoimmune response, and also IBD. Genetic modification of MSCs to overexpress HIF-1, IFN-y, and IL-35 exhibited great potential to raise MSCs' anti-inflammatory and pro-regeneration capabilities.

Gaps:

- The detailed molecular pathways targeted by genetic interventions remain to be established, such as ICAM-1, Nrf2/ARE.
- Poor understanding of the interaction of genetically modified MSCs with immune cells and the gut microenvironment.

Key Questions:

- How do specific genetic manipulations, such as ICAM-1 or Nrf2/ARE, modulate the MSC signaling pathways to exert anti-inflammatory effects and tissue repair?
- Can genetic manipulations improve the interactions of MSCs with gut microbiota for better therapeutic outcomes?

Stem Cell Research Challenges

Stem cells are an evolving area of research that is riddled with multiple unknowns. The method of application (i.e., direct endoscopic injection), how to perform first-in-human testing, and in what IBD subgroup this will be relevant are key questions. Importantly, there is a question surrounding the potential immunogenicity of transplant medium. Some research groups have transitioned transplant medium toward using substances such as fibrin, which is already licensed for human use, and hydrogel, which can be readily genetically altered and can adapted to mimic the gastrointestinal microenvironment[2].

Gaps:

- Limited understanding of how stem cell modifications affect interactions with the immune system.
- Absence of robust methods that will predict or prevent unexpected differentiation and/or proliferation upon transplantation.

Key Questions:

- How do stem cells promote repair and regeneration beyond differentiation-possibly via exosomes, cytokines?
- Can we identify and improve the key signaling pathways responsible for therapeutic effects?

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Immunological Rejection

A major challenge with stem cell transplants is rejection by the recipient's immune system. To evade tissue rejection, patients undergo immunosuppressive treatment, that makes them susceptible to microbial infections. Inducing pluripotent cells directly from the patient's cells to generate graft or tissue may resolve the problem associated with immunological rejection to an extent. However, the low frequency of iPSCs is a major hurdle. It is clear that CD patients are at higher risk of infection compared to those who undergo transplantation to treat cancer or other diseases that do not involve the intestinal tract[4]. During SC mobilization, patient immunity is reduced, and the risk of infection is higher. Therefore, patients should be carefully nursed during mobilization and reasonable drug levels should be prescribed to reduce the development of adverse reactions.

Gaps:

- There is presently no effective method of minimizing the risk of infection without compromising the required immunosuppression in recipients of stem cell transplantation
- The low efficiency in generating patient-specific iPSCs for autologous stem cell therapies is one major bottleneck that seriously limits their wide applications and clinical uses.

Key Questions:

- How can the generation of iPSCs from patient cells be further optimized for their greater availability and effectiveness in therapy?
- Can personalized medicine or precision approaches be employed to establish optimal immunosuppressive therapy in the individual patient?

Safety

Stem cells being used in cell therapy or regenerative medicine could be exposed to microbes, which eventually could cause infectious diseases. The necessary preliminary diagnostic test must be developed before the treatment. In addition, retaining intended biological activity before treatment is crucial for the success of the therapy. Systematic protocols need to be developed for isolation, testing, and transplantation of stem cells, to ensure patients' safety.

Key Questions:

- How do we develop diagnostic tests for the detection of microbial contamination of stem cell preparations before transplantation?
- How do we develop uniform practices for safe stem cell isolation, testing, and transplantation?

Hypothesis

Genetic modifications in human iPSCs using CRISPR-Cas9 gene editing technology

Synergistic advances in relevant scientific fields provide new directions for research toward (Human Intestinal Organoid (HIO)) clinical translation—namely CRISPR (clustered regularly interspaced short palindromic repeats) for gene editing and metabolic programming. In cystic fibrosis, the first successful CRISPR-based gene correction was reported in gut organoids from cystic fibrosis patients. In colorectal cancer, CRISPR/Cas9 is exploited to develop a closer human colorectal cancer model using HIOs. Both examples provide a scientific opportunity to modify the IBD ISC genetic susceptibility (for example, in NOD2 mutations in Paneth cell dysfunction in CD) and to develop a human IBD epithelial experimental model with the ability to perturb and interrogate function with gene editing[2]. Gene editing technology with big-data analysis of transcriptome and proteome analysis is essential prior to undertaking clinical applications, in order to produce safe, reproducible, and cost-effective products that must be the goal for both standardized and optimized products. We reason that one promising solution is to introduce desired genetic modifications in human iPSCs using i.e., the CRISPR-Cas9 gene editing technology, followed by differentiating the genetically edited iPSCs into MSCs. To develop cell therapeutics with gene-edited stem cell lines, it is vital to develop and maintain safety standards with criteria that include precise off-target checks, high efficiency, and reproducibility of data.

Human Intestinal Organoid (HIO)

How widely applicable HIOs are in the real-world clinic is unclear, given the present early stage of research[2]. We envisage several hypothetical clinical scenarios in which HIOs might be relevant: (1) in medically refractory IBD with significant gut damage; (2) in early postoperative recurrence of CD with localized inflammation in the operative anastomosis; (3) in fibrostenosing CD, in which animal studies have provided some data to suggest benefit. Organoid technology is a perceptible advance in translational science and the vision of using HIOs as a tissue repair approach in IBD.

Conclusion

Inflammatory Bowel Disease (IBD), including Crohn's Disease (CD) definitely needs more effective treatments as current therapies are only aimed at controlling inflammation. Stem cell therapies are promising for regenerative and immunomodulatory properties with potential in tissue repair and immune regulation in CD. SCs inhibit pro-inflammatory cytokines, including

IFN-γ, TNF-α, and IL-17, while enhancing anti-inflammatory cytokines such as IL-10 and IL-4. This shifts the balance towards Th1/Th2/Th17. These immunomodulatory effects can be mediated through soluble factors like TGF-β, IL-10, and IDO, which could inhibit dendritic cell activity and T-cell function, thus inducing Treg proliferation. They contribute to mucosal healing and intestinal regeneration through increased proliferation of epithelial cells and improved intestinal barrier, particularly by promoting ISCs activity that is very crucial in mucosal regeneration. Preclinical models have looked into several types of stem cells, including MSCs and HSCs, and showed positive results in targeting chronic inflammation and promoting repair of the intestinal barrier. Clinical trials for both autologous and allogeneic stem cell treatments for CD have been promising. Autologous stem cell therapies, including AT-MSCs and BM-MSCs, proved to be safe and effective in reducing disease activity, healing fistulas, and inducing remission with minimal side effects. Allogeneic stem cell treatments, including expanded AT-MSCs and UC-MSCs, were also effective in reducing disease activity, improving fistula healing, and providing long-term clinical remission. Overall, these studies highlight the potential of stem cell therapies in treating refractory CD and related complications. Clinical trials have provided valuable insights into the potential applications and efficacy of SC therapy for CD/IBD. However, it is important to acknowledge the limitations of current SC therapy, including its efficacy, technology, and safety. Obtaining a large number of high-quality, homogeneous SC preparations remains technically challenging. Safety concerns associated with SC therapy include microcirculatory and coagulation dysfunction, immune rejection, and the risk of tumor formation. Several modifications have been proposed to enhance the use of SC therapy, such as changes to the culture conditions and cultivation methods for SCs, modification of SC contents and genetic genes, and extraction of SC derivatives. These strategies can potentially optimize SC therapy and improve its efficacy and safety in treating CD/IBD. These next-generation SCs are being used as 'Trojan horses' to improve the delivery of drugs and oncolytic viruses to target tissues and are also being engineered with angiogenic, neurotrophic, and anti-inflammatory molecules to accelerate the repair of injured or diseased tissues. Here we reviewed whether SC therapy can improve CD. It is evident that SC transplantation reduces gut inflammation and improves the quality of life. However, more high-quality randomized controlled clinical trials and basic research are required.

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