



Stem cell- and extracellular vesicle-based therapies for perianal fistulizing Crohn's disease: An updated review

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Abstract

Perianal fistulizing Crohn's disease (PFCD) is a complication of CD that significantly impacts patients' quality of life, particularly their social and sexual well-being. Despite advances in therapy, its treatment remains a major challenge in the field of inflammatory bowel disease. The pathogenesis of PFCD involves increased production of inflammatory cytokines by infiltrating macrophages and lymphocytes, stimulation of the epithelial-to-mesenchymal transition, activation of myofibroblasts, and elevated levels of matrix metalloproteinases. Mesenchymal stem cells (MSCs) are multipotent stromal cells with self-renewal and differentiation capabilities. Evidence from animal models and clinical trials indicates that MSC injection into PFCD lesions suppresses the infiltration of inflammatory cells and cytokines, resulting in complete fistula healing. More recently, MSC-derived extracellular vesicles (EVs) have shown promising results in promoting fistula healing, particularly in cases of refractory or relapsing fistulas. Notably, the activation of macroautophagy (hereafter referred to as autophagy) in MSCs has been shown to accelerate the healing process. This narrative review discusses the mechanisms underlying PFCD pathogenesis, the therapeutic roles of MSCs and their EVs, and the potential role of autophagy upregulation in enhancing MSC function and EV production.

Key Words: Mesenchymal stem cells; Crohn's disease; Perianal fistulizing Crohn's disease; Extracellular vesicles; Exosomes; Autophagy

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Core Tip: Perianal fistulizing Crohn's disease (PFCD) is a severe complication of CD, characterized by the accumulation of inflammatory cells and elevated cytokine production. Although various medical and surgical approaches aim to control this disease, recurrence remains a major challenge. Both animal models and clinical trials have shown that mesenchymal stem cells (MSCs) and their extracellular vesicles (EVs) can reduce inflammation and promote healing in refractory PFCD effects that may be further enhanced by autophagy activation. This review highlights the therapeutic potential of MSCs and their EVs in PFCD treatment and explores the supportive role of autophagy in enhancing their efficacy.

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INTRODUCTION

Perianal fistulizing Crohn's disease (PFCD) is a chronic, complex inflammatory anomaly affecting the internal bowel wall, characterized by abnormal anatomical communications between two epithelialized surfaces in the perineal region. This painful and debilitating condition affects approximately 20% of patients with CD worldwide, with one-third experiencing recurrent fistula formation despite advanced medical interventions and treatments. Clinical examinations and diagnostic tools such as endoscopy, magnetic resonance imaging (MRI), endoanal ultrasound, computed tomography, and fistulography have revealed limited insights into the pathogenesis of Crohn's-associated fistulae[1]. Moreover, the lack of robust *in vitro* and *in vivo* models impedes the development and evaluation of novel therapies. Without reliable disease models, understanding PFCD pathogenesis and assessing the efficacy and safety of potential treatments remain significant challenges.

PFCD can cause significant discomfort, recurrent infections, and complications that severely impact patients' quality of life, often leading to embarrassment and psychological distress. Treatment typically involves a combination of medical and surgical approaches, which are expensive and frequently complicated by high recurrence rates. Therefore, there is a pressing need for more effective and sustainable alternatives, such as stem cell-based therapies[1,2].

METHODOLOGY AND REVIEW CRITERIA

This submission is a narrative minireview that provides a concise synthesis of recent preclinical and clinical studies on the use of mesenchymal stem cells (MSCs) and extracellular vesicles (EVs) in PFCD. It is based on a curated selection of relevant literature from the past 10 years, highlighting current trends and key findings in the field. The databases consulted include PubMed, Google Scholar, the Directory of Open Access Journals, ScienceDirect, and others. The search was done using the above-mentioned keywords.

MECHANISMS OF PFCD: INTERPLAY BETWEEN INFLAMMATION AND EPITHELIAL-TO-MESENCHYMAL TRANSITION

Current state-of-the-art research on the molecular mechanisms of fistulizing CD highlights the pivotal role of epithelial-to-mesenchymal transition (EMT) in the pathophysiology of fibrosis and fistula formation[3]. EMT is a complex biological process in which epithelial cells lose their defining characteristics, such as polarity, intercellular adhesion, and tight junction integrity and acquire mesenchymal features, including enhanced motility, invasiveness, and extracellular matrix (ECM) production. This transformation is driven by the downregulation, relocalization and degradation of tight junction and adherens junction proteins, including claudins, occludin, zona occludens-1, and E-cadherin[4]. Loss of E-cadherin at adherens junctions leads to the release of β -catenin and p120-catenin, which translocate to the nucleus and regulate gene transcription, particularly under the influence of the Wnt/ β -catenin signaling pathway[5]. Simultaneously, decreased expression of connexins disrupts gap junction-mediated intercellular communication. As EMT progresses, repression of junctional proteins is reinforced by EMT-inducing transcription factors such as Snail, Slug, ZEB1/ZEB2, and Twist, thereby consolidating the mesenchymal phenotype[6]. This phenotypic shift is associated with the upregulation of mesenchymal markers, including fibroblast-specific protein 1, smooth muscle actin, N-cadherin, and fibronectin, which collectively contribute to tissue remodeling and fibrotic fistula formation in PFCD[7].

The EMT process is tightly regulated by several other molecular mediators, including members of the transforming growth factor-beta (TGF- β) family, tyrosine kinase receptors, non-coding RNAs, and context-specific transcription factors [1,2]. These regulatory elements interact in a tissue- and context-dependent manner to modulate EMT activation and progression.

In addition to EMT-driven fibrosis, PFCD lesions exhibit prominent immune cell infiltration, underscoring the inflammatory dimension of this disease. Histopathological investigations have shown that over 56% of PFCD cases demonstrate severe acute inflammation[8]. Immunohistochemical analysis reveals a disease-specific immune profile: PFCD-associated fistulae are characterized by dense infiltration of cluster of differentiation 45RO⁺ memory T cells and a narrow band of cluster of differentiation 68⁺ macrophages lining the inner wall, whereas cluster of differentiation 20⁺ B cells are localized to the outer wall. These immune cell distribution patterns are consistent across fistulae regardless of location or depth, highlighting a distinct immunological signature associated with CD[9].

T cell subsets, particularly Th1 and Th17 cells, also play a central role in the pathogenesis of PFCD by producing pro-inflammatory cytokines such as interleukin (IL)-12, interferon- γ , IL-23, and tumor necrosis factor (TNF)- α , which initiate and sustain immune activation and mucosal injury[10]. TNF- α is pivotal in this process, inducing the expression of TGF- β , a key mediator in EMT. Thereafter, TGF- β activates transcription factors such as Snail1 and Slug, which repress E-cadherin expression, thereby enhancing cellular invasiveness and promoting fistula formation[11]. In addition, TNF- α stimulates the expression of *ETS1* and β 6-integrin, which enhance cell migration and invasiveness, processes which are essential to EMT[12]. Furthermore, TNF- α contributes to the secretion of IL-13, which in turn promotes further EMT through an autocrine loop within the fistula tract, perpetuating inflammation. IL-34 also exacerbates inflammation by inducing TNF- α and IL-6 *via* extracellular regulated protein kinases signaling and promoting the release of *CCL20*, a chemokine that facilitates immune cell recruitment to active lesions. Moreover, B cells, influenced by cytokines such as IL-2 and IL-21, differentiate into plasma cells producing granzyme B, which damages the epithelial tissue and contributes to the ongoing inflammatory process[13].

Metalloproteinases (MMPs) play a crucial role in the pathogenesis of PFCD by mediating the degradation and remodeling of the ECM, which is essential for fistula formation. Elevated MMP activity, particularly MMP-3, MMP-9, and MMP-13, is found in fistula tissue and contributes significantly to tissue destruction and inflammation. MMP-3, primarily produced by mononuclear cells and fibroblasts, and MMP-9, localized in granulocytes, are associated with active inflammation in fistulae. MMP-13, which is largely absent in non-fistula CD tissue, contributes to collagen breakdown, exacerbating ECM degradation[14]. This dysregulated MMP activity is compounded by decreased levels of tissue inhibitors of MMPs (TIMPs), such as TIMP-1, TIMP-2, and TIMP-3, which normally act to regulate MMP function. The imbalance between MMPs and TIMPs results in uncontrolled ECM degradation, promoting chronic inflammation, fibrosis, and persistent fistula formation. Additionally, MMPs are involved in the activation of fibroblasts and myofibroblasts, which further perpetuate the inflammatory cycle and fibrosis[14,15]. Thus, MMPs contribute not only to the structural remodeling of tissue but also to the chronic inflammation and fibrosis that characterize PFCD, highlighting their critical role in fistula pathogenesis (Figure 1).

Genetic predisposition plays a key role in the development of PFCD. In patients with CD, mutations in the *NOD2* gene disrupt intestinal microbiota homeostasis and promote excessive gut inflammatory responses, contributing to fistula formation. Additionally, mutations in autophagy-related genes such as *ATG16 L1* and *IRGM* are strongly associated with CD pathogenesis. Notably, *NOD2* also functions as a key autophagy inducer by recruiting *ATG16 L1* to the plasma membrane[16].

STEM CELL THERAPY IN PFCD

Treatment for Crohn's perianal fistula consists of a combination of medical and surgical therapies. However, treatment options are limited and characterized by high recurrence rates after both approaches. Thus, more effective alternative treatments are necessary.

MSC treatment has emerged as a promising strategy to reinforce surgical closure of the internal opening in patients with complex Crohn's perianal fistulas. This approach emphasizes the ability of stem cells to modulate inflammatory processes and promote tissue reconstruction.

In line with this, patients with medical therapy-refractory Crohn's perianal fistulas, with a previous history of failed anti-TNF treatment and surgical closure, were treated with a single intralesional dose of a cell suspension containing 120×10^6 cells (expanded adipose-derived stem cells). The treatment involved injecting the first half of the dose around the sutured internal openings through the anal canal, and the remaining half was injected into the tract wall along the fistula through the external openings. Results showed more than 40% radiological remission and 70% clinical closure. Additionally, MSC therapy significantly improved the overall quality of life of patients[17].

Furthermore, the effectiveness of darvadstrocel, an adipose-derived MSC particularly used in treating complex perianal fistulas associated with CD, was reported in a recent study. Fourteen patients received a single injection of darvadstrocel. After a median follow-up of 92 weeks, 57.1% achieved successful fistula closure. The treatment was considered safe with no perioperative complications reported. Therefore, darvadstrocel represents a minimally invasive and promising option for the management of perianal fistulas, achieving clinical success in approximately half of the patients[18]. In a meta-analysis of clinical trials, MSCs significantly outperformed conventional therapies in short-, long-, and extended healing phases, although no significant advantage was observed in the medium term. Subgroup analyses revealed that variations in cell type, source, and dosage did not significantly impact efficacy, suggesting the treatment's robustness across different formulations. Notably, MSC therapy was more effective against CD-related fistulas compared to cryptoglandular fistulas, highlighting the potential immunomodulatory benefits in this treatment modality. Overall, MSC transplantation provides a safe, effective, and durable treatment option, yielding consistent outcomes regardless of specific MSC characteristics[19]. Figure 1 illustrates the therapeutic roles of MSCs in PFCD.

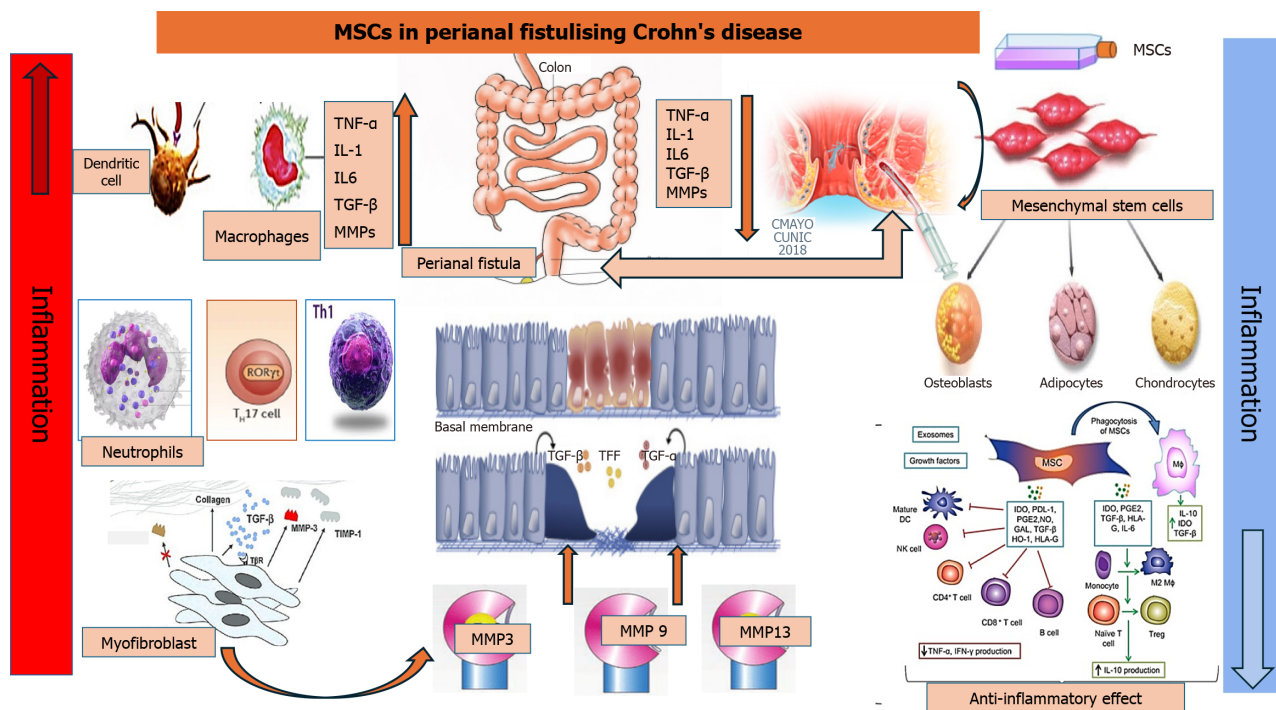


Figure 1 Mechanisms of perianal fistulizing Crohn's disease and therapeutic roles of mesenchymal stem cells[2]. Enhanced production of inflammatory cytokines by infiltrating macrophages and other inflammatory cells stimulates the epithelial-to-mesenchymal transition, resulting in activation of myofibroblasts and elevation of matrix metalloproteinases, leading to fistula formation. Injection of mesenchymal stem cells into the fistula results in suppression of the inflammatory cells and cytokines and complete resolution of perianal fistulizing Crohn's disease. MSCs: Mesenchymal stem cells; TNF: Tumor necrosis factor; IL: Interleukin; TGF: Transforming growth factor; MMP: Matrix metalloproteinase; Th: T helper cells; TFF: Trefoil factor family; DC: Dendritic cell; NK: Natural killer; CD4: Cluster of differentiation 4; Treg: Regulatory T cell; IDO: Indolamine 2,3-dioxygenase; PDL-1: Programmed death ligand 1; PGE2: Prostaglandin E2; NO: Nitrogen oxide; GAL: Gallic acid; HO-1: Heme oxygenase-1; HLA: Human leukocyte antigen. Citation: Bhatnagar P, Elhariri S, Burud IAS, Eid N. Perianal fistulizing Crohn's disease: Mechanisms and treatment options focusing on cellular therapy. *World J Gastroenterol* 2025; 31: 100221. Copyright ©The Author(s) 2025. Published by Baishideng Publishing Group Inc.

A systematic review and meta-analysis by Guillo *et al*[20], which included 25 studies involving 596 patients, demonstrated that MSC therapies are effective in treating refractory PFCD. The remission rates were 36.2% after 3 months and 57.9% after 6 months, with MSC therapy being significantly more effective compared to placebo. This study also suggested that both adipose-derived and bone marrow-derived stem cells showed significant therapeutic efficacy.

The long-term application of MSC therapy in 24 patients with PFCD was investigated for five years. After five years of follow-up and treatment, 54.2% of patients showed clinical remission, and 25% showed sustained clinical response. Radiologically, 75% of patients experienced improvement within the first 12 months, with 37.5% demonstrating long-term improvement and 16.7% achieving complete healing. Additionally, 58.3% of patients did not require additional surgeries, and no adverse events or long-term incontinence were reported. These findings confirm MSC therapy as a promising treatment for PFCD, providing durable clinical benefits and safety over the long term[21]. A summary of stem cell-based therapies in PFCD is shown in Table 1[20-33].

Clinical trials using MSCs for PFCD vary in cell sources, with some employing adipose-derived MSCs (ADSCs) (*e.g.*, Pronk *et al*[17], 120×10^6 cells) and others using bone marrow-derived MSCs (BM-MSCs) (*e.g.*, Swaroop *et al*[23], Lightner *et al*[24], 75×10^6 cells). ADSCs are easier to harvest and may offer stronger anti-inflammatory effects, while BM-MSCs show more durable responses. Doses range from 75-120 million cells, with diverse delivery methods and endpoints (*e.g.*, clinical closure *vs* MRI-confirmed remission), complicating comparisons. Most trials only partially align with the 2023 CONSORT extension for cell therapy, often lacking in product characterization and immune safety data[34]. Our review underscores the therapeutic potential of MSCs for PFCD while highlighting the need for standardized protocols to improve trial reproducibility, comparability, and regulatory acceptance[17,19,23,24,29,31].

EVS AS AN EMERGING THERAPY FOR PFCD

Mammalian cells secrete EVs containing proteins, lipids and functional nucleic acids (messenger RNA, microRNA, and other RNA species) for cellular communication and uptake both *in vitro* and *in vivo*. EVs are categorized based on size into two primary subsets: Exosomes (50 nm-100 nm in diameter), which have an endosomal origin, and micro-vesicles (100 nm-1000 nm in diameter), derived from cytoplasmic budding[2]. Interestingly, EVs can also be derived from plants [35].

Table 1 Summary of stem cell-based therapies in perianal fistulizing Crohn's disease[20-33]

	Stem cells/sources	Clinical/preclinical trials	Year	Duration of study	Key findings	Ref.
1	MSCs (sourced from bone marrow or adipose tissue)	Clinical trial II and III	2025	Up to 52 weeks	Complete fistula closure was observed in 71% of PFCD patients	Guillo <i>et al</i> [20]
2	MSC therapy	Clinical, radiological and patient-reported	2025	60 months	5 years patients experienced sustained radiological healing (16.7%)	Anand Mr <i>et al</i> [21]
3	Allogeneic adipose-derived MSCs	Real-world, observational cohort study	2024	14 months	61% of patients achieved and maintained clinical remission	White <i>et al</i> [22]
4	Allogeneic bone marrow-derived mesenchymal stromal cells	Open-label, phase I/II, single-arm study	2024	Up to 104 weeks	70% achieved fistula response ($\geq 50\%$ decrease in drainage) after 24 weeks	Swaroop <i>et al</i> [23]
5	Bone marrow-derived MSCs	3-phase IB/IIA randomized, placebo-controlled, single-blinded trials (perianal, rectovaginal, ileal pouch fistulas)	2024	12 months	67.7% perianal, 37.5% rectovaginal, and 46.2% peripouch fistula healing after 12 months	Lightner <i>et al</i> [24]
6	Allogeneic expanded adipose-derived stem cells (Cx601)	Phase III randomized, double-blind, placebo-controlled clinical trial	2018	52 weeks	56.3% combined remission and 59.2% clinical remission after 1 year	Panés <i>et al</i> [25]
7	Allogeneic adipose-derived stem cells (ADSCs, Cx601, Darvadstrocel, Alofisel®)	Clinical application and mechanistic review	2021	Not specified	ADSCs showed strong anti-inflammatory, immunomodulatory, anti-apoptotic, and pro-angiogenic properties, were superior to BM-MSCs in several ways, effective in refractory Crohn's perianal fistulas, Cx601/Alofisel approved by EMA	Buscail <i>et al</i> [26]
8	Human amnion epithelial cells	Phase I open-label clinical trial	2023	52 weeks	Complete response in 4/10 patients, partial response in 4/10, significant improvements in fistula healing	Keung <i>et al</i> [27]
9	Stem cell transplantation with or without anti-TNF therapy	Retrospective clinical cohort study	2024	66 months	76.9% complete closure, anti-TNF therapy did not significantly improve closure rates	Park <i>et al</i> [28]
10	Allogeneic adipose-derived stem cells	Multicenter, open-label, dose-escalation pilot study	2016	8 weeks	Complete closure in 3 out of 6 patients, closure sustained up to 8 months	Park <i>et al</i> [29]
11	HESC-derived MSCs	Canine anal furunculosis in dogs	2016	6 months	HESC-MSCs were well-tolerated, reduced IL-2 and IL-6 levels, complete fistula healing after 3 months, partial relapse in 2 dogs after 6 months	Ferrer <i>et al</i> [30]
12	Adipose-derived allogeneic stem cells	Open-label clinical trial on dogs with refractory spontaneous perianal fistulas	2024	12-48 months	100% fistula closure after 1 month	Enciso <i>et al</i> [31]
13	Human bone marrow-derived mesenchymal stem cells	Animal study (SAMP-1/YitFc murine model of chronic small intestinal inflammation)	2024	28 days	HMSCs inhibited naive T cell proliferation <i>via</i> PGE2, reprogrammed macrophages to an anti-inflammatory phenotype, promoted early mucosal healing, achieved complete mucosal, histological, immunologic, and radiological healing by day 28	Dave <i>et al</i> [32]
14	Mesenchymal stromal cells from adipose tissue, bone marrow, or umbilical cord	Preclinical (not specified)	2014		MSC therapy (both autologous and allogeneic) is safe and potentially effective for refractory fistulizing CD, with ongoing phase III trials. MSCs show immunomodulatory effects	Liew <i>et al</i> [33]

MSCs: Mesenchymal stem cells; PFCD: Perianal fistulizing Crohn's disease; ADSC: Allogeneic adipose-derived stem cell; BM-MSC: Bone marrow-derived mesenchymal stem cell; EMA: European Medicines Agency; TNF: Tumor necrosis factor; HESC: Human embryonic stem cell; IL: Interleukin; HMSC: Human bone marrow-derived mesenchymal stem cell; PGE2: Prostaglandin E2; CD: Crohn's disease.

The use of MSC-derived EVs for the treatment of PFCD offers several advantages over MSCs, including lower immunogenicity, reduced risk of tumor formation, and more accessible storage and handling requirements[36,37]. Mechanistically, EVs exert their effects *via* pathways like MSCs in the treatment of PFCD, as described above. The potential of combining MSC or EV therapy with conventional medical treatments (*e.g.*, antibiotics, thiopurines, tacrolimus, and anti-TNF agents) to reduce the duration of therapy in PFCD warrants further investigation.

EVs are commonly isolated using ultracentrifugation, which can process large volumes but may co-isolate contaminants and require costly equipment; size-exclusion chromatography, which offers higher purity and structural preservation but has limited reproducibility; or immunoaffinity capture, which enables highly specific subpopulation isolation based on surface markers, though it is expensive and yields low quantities. For characterization, nanoparticle tracking

analysis measures size distribution and concentration but can be influenced by impurities, while transmission electron microscopy (TEM) provides high-resolution imaging of EV morphology (e.g., double-membrane structures) but is technically demanding. Western blotting confirms EV identity through protein markers, and flow cytometry assesses surface markers and heterogeneity, although its sensitivity for small EVs is limited. These limitations highlight the need for complementary techniques in EV research[35-37].

A few clinical studies using EV therapy in PFCD human patients demonstrated healing success, with no reported recurrence. A phase I clinical trial demonstrated that local injection of cord MSC-derived exosomes (5 mL of a 50 µg/mL solution) into five patients with refractory PFCD resulted in high efficacy fistula healing within six months, and no reported complications based on MRI imaging[38]. In a phase II clinical trial, the efficacy of MSC-derived exosomes was tested in 23 patients with refractory perianal fistulas in CD. After three local injections of exosomes, 60% of patients showed complete fistula closure, and 69.7% of the treated fistula tracts closed completely. Histopathological analysis showed reduced inflammation and enhanced tissue regeneration[39]. The exosomes were isolated using ultracentrifugation and assessed for quality *via* TEM and Western blot analysis of specific markers such as cluster of differentiation 63, cluster of differentiation 81, and cluster of differentiation 99. A very recent study explored the use of locally injected MSC-derived EVs delivered *via* a nanofiber-hydrogel composite (NHC) in a rat model of PFCD. Post-injection MRI revealed reduced fistula inflammation and enhanced healing, attributed to sustained EV release from the NHC, macrophage polarization, and neovascularization[40].

Plant-derived EVs have been investigated for the treatment of inflammatory bowel disease (IBD) in animal models. Compared to mammalian-derived EVs, they offer advantages such as improved safety, lower cost, greater availability, and reduced risk of adverse immune reactions[41,42]. Red cabbage-derived EVs (Rabex) have been investigated and engineered as potential therapeutic agents for the treatment of IBD in animal models. Rabex exhibited dual functions: Suppressing inflammation in macrophages and promoting regeneration of colonic epithelial cells[42]. However, studies comparing the efficacy of plant- and mammalian-derived EVs in PFCD are still lacking.

The widespread clinical application of MSCs and EVs in PFCD is limited by several challenges. These include the absence of standardized protocols for their isolation, characterization, and quality control. Moreover, high costs, inconsistent dosing strategies, and variations in administration routes (local *vs* systemic) further complicate their clinical use[17,19,20,36-40]. Addressing these issues through standardization is essential to support broader and more effective therapeutic implementation.

AUTOPHAGY ACTIVATION IN MSCS FOR IMPROVED EFFICACY OF PFCD TREATMENT

Macroautophagy (hereafter referred to as autophagy) is a prosurvival process that clears damaged cellular components in response to stress such as oxidative stress, inflammation, and hypoxia. It is initiated by mammalian target of rapamycin (mTOR) inhibition and adenosine 5'-monophosphate-activated protein kinase activation and completed through the action of autophagy-related genes (*ATG1-ATG13*). Autophagy is characterized by the formation of *ATG8*/microtubule-associated 1A/1B light chain 3 (LC3)-mediated autophagosomes that enclose cellular components, which subsequently fuse with lysosomes to form autolysosomes for degradation[43,44]. In inflammatory diseases such as CD, upregulated autophagy in MSCs may enhance their survival and functional capacity in hostile environments[2,45,46].

Recent *in vitro* investigations have reported that autophagy upregulation in MSCs by rapamycin (mTOR inhibitor) enhanced MSC-induced suppression of inflammatory cluster of differentiation 4⁺ T cells *via* secretion of TGF-β1. Moreover, autophagy was found to play an important role in the differentiation of MSCs at the cellular and molecular levels, thereby influencing their therapeutic potential across a wide range of diseases, including PFCD[46,47]. In addition, the pro-autophagic effects of metformin were found to enhance the stemness of MSCs, improving both the quantity and composition of MSC-derived exosomes[48].

Importantly, autophagy-related genes are essential for EV biogenesis *via* secretory (non-degradative) autophagy, particularly in exosome formation *via* multivesicular body formation, and ultimately exosome release. Genetic disruption of the *ATG12-ATG3* conjugation impairs late endosome trafficking and EV production. Additionally, LC3-dependent EV loading and secretion has been identified as an exosome-like secretory pathway[49-52]. Accordingly, activation of autophagy in MSCs may enhance both the quality and quantity of EVs, potentially accelerating PFCD healing (Figure 2).

CONCLUSION

A growing body of evidence suggests that PFCD is a severe complication of CD that significantly impairs patients' quality of life. Despite therapeutic advances, treatment remains challenging. MSCs and their EVs have shown promise in promoting perianal fistula healing in animal models and clinical trials. Notably, autophagy activation in these cells enhances their function and EV production, accelerating the healing process. However, standardization of EV isolation, quality control, dosing, delivery routes, and cost remains lacking. Further studies in animal models of PFCD and large-scale human trials are needed to validate the therapeutic potential of EVs. Additionally, the efficacy of plant-derived EVs in PFCD, in comparison to their mammalian-derived counterparts, warrants investigation.

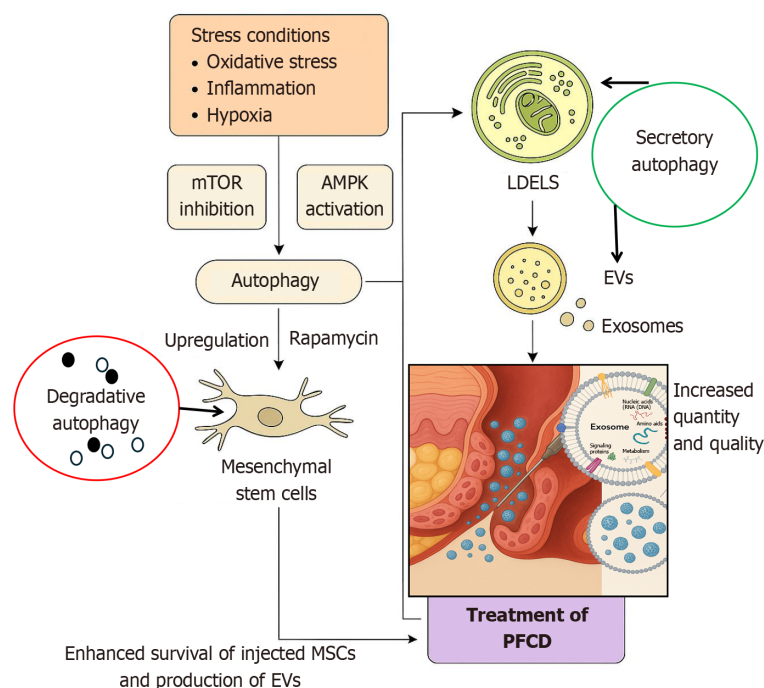


Figure 2 Upregulation of degradative and secretory autophagy in mesenchymal stem cells promotes their survival and enhances both the quality and quantity of their extracellular vesicles, including exosomes. Light chain 3 (LC3)-dependent extracellular vesicle (EV) loading and secretion, LC3-dependent EV loading and secretion, lysosome, autophagosome. mTOR: Mammalian target of rapamycin; AMPK: Adenosine 5'-monophosphate-activated protein kinase; MSCs: Mesenchymal stem cells; EV: Extracellular vesicle; LDELS: Light chain 3-dependent extracellular vesicle loading and secretion; PFCD: Perianal fistulizing Crohn's disease.

FOOTNOTES

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