

Nanoparticle-Mediated PPAR Modulation of Macrophage Polarization in Radiation Enteritis: A Narrative Review

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Abstract: Radiation enteritis (RE) is a frequent and clinically important adverse effect of abdominal radiotherapy, characterized by acute inflammatory injury and longer-term fibrotic remodeling of the intestinal tract. Most patients receiving pelvic or abdominal irradiation experience measurable worsening of intestinal function. Macrophages orchestrate RE pathogenesis: tissue injury initially triggers a pro-inflammatory M1 phase that amplifies damage, followed by an M2 phase that promotes repair. Peroxisome proliferator-activated receptors (PPARs) have emerged as key regulators of macrophage polarization, with PPAR γ playing a prominent role in promoting anti-inflammatory and tissue-restorative responses. This review explores the molecular mechanisms linking macrophage polarization and PPAR signaling in RE, reviews current PPAR-targeted therapies, and describes nanotechnology-based strategies for targeted intestinal delivery of PPAR modulators. We discuss how PPAR agonists modulate immune responses and how formulations engineered for localized intestinal activity may reduce systemic adverse effects. We also highlight progress in nanoparticle design, including carriers responsive to pH or reactive oxygen species and ligand-coated systems (e.g. hyaluronic acid or mannose) that target macrophages, thereby enhancing therapeutic delivery and cellular uptake. Finally, we summarize emerging omics-based approaches (single-cell transcriptomics, spatial profiling, and artificial-intelligence-driven design) that are accelerating the identification of novel therapeutic targets and informing the development of precision nanomedicines for RE.

Keywords: radiation enteritis, PPAR, macrophage, nanoparticle drug delivery, targeted nanotherapy

Introduction

Radiation enteritis (RE) is an inflammatory injury of the intestine secondary to abdominopelvic radiotherapy for malignancy. Acute gastrointestinal toxicity remains common after pelvic irradiation. In a prospective randomized double-blind placebo-controlled study of 234 patients receiving pelvic radiotherapy, grade 1 and grade 2 radiation-induced enteropathy occurred in 56%–64% and 22%–26% of patients, respectively.¹ Chronic bowel injury also remains clinically relevant: in the updated Phase III NRG Oncology-RTOG 1203 trial, one year after radiotherapy, frequent diarrhea persisted in 15.1% of patients treated with conventional pelvic radiotherapy versus 5.8% of those treated with IMRT, and greater antidiarrheal use also remained more common in the conventional RT arm.² In China, for example, >61% of patients with pelvic cancer receive therapeutic irradiation, with 75% experiencing acute intestinal injury and 5%–20% developing late effects.³ Complementing these clinical data, translational evidence has demonstrated chronic low-grade inflammation, mucus barrier disruption, and bacterial infiltration in irradiated intestinal mucosa up to two decades after pelvic radiotherapy, supporting a biological basis for persistent or late RE.⁴ Recent qualitative evidence further suggests that chronic bowel symptoms after pelvic radiotherapy remain under-recognized and insufficiently addressed in survivorship care, despite their substantial impact on quality of life.⁵

The condition can cause severe malabsorption, bleeding, and life-threatening complications, imposing a substantial burden on survivors' quality of life.

RE results from radiation-induced DNA damage and epithelial cell death in the rapidly proliferating intestinal mucosa, accompanied by oxidative injury and maladaptive immune responses. Although advances in endoscopic and radiologic techniques facilitate diagnostic confirmation of RE, their value for preemptive therapeutic intervention remains limited. No approved curative therapies exist to prevent or reverse radiation injury; clinical management is largely palliative (eg., fluid support, dietary modification, antidiarrheals, corticosteroids), with surgery reserved for complications that arise. Therefore, there is an urgent need for molecularly targeted therapies that modulate the radiation response and accelerate mucosal healing. Macrophages are well-established mediators of intestinal homeostasis and inflammation. Tissue-resident and recruited macrophages span a functional spectrum that is often categorized into pro-inflammatory M1 and anti-inflammatory/wound-healing M2 phenotypes.⁶ This M1/M2 balance is a key determinant of whether tissue injury resolves or progresses to chronic fibrosis. After radiation injury, ionizing radiation skews macrophage polarization toward an M1 phenotype, triggering a pro-inflammatory cytokine cascade (eg., TNF- α , IL-1 β , and IL-6) and increasing reactive oxygen species production, thereby exacerbating mucosal damage. In contrast, M2 macrophages secrete IL-10, TGF- β , and growth factors that support epithelial repair and dampen inflammation.^{7,8} Accordingly, suppressing M1 activity while promoting M2 polarization represents a promising therapeutic strategy.

Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptors that regulate transcriptional programs involved in metabolism and inflammation.⁹ Among them, PPAR γ is highly expressed in macrophages and plays a central role in macrophage polarization. PPAR γ agonists attenuate inflammatory responses in colitis models, suggesting that targeting PPAR signaling in macrophages may ameliorate RE. In addition, nanotechnology-based drug delivery systems can improve tissue specificity. Nanoparticles (NPs) can be engineered to encapsulate PPAR-modulating agents, enhance their stability, and selectively target the inflamed gut or intestinal macrophages.⁶ In the following sections, we review the roles of macrophages in RE, PPAR signaling mechanisms in macrophages, current PPAR-targeted therapies for intestinal inflammation, and emerging nanodelivery approaches designed for precise intervention in radiation enteritis.

Macrophage Polarization in Radiation Enteritis

Macrophages are plastic innate immune cells that adopt distinct phenotypes in response to microenvironmental cues. They are broadly categorized as M1 (classically activated) and M2 (alternatively activated), each with characteristic markers and functions¹⁰ (Figure 1). M1 macrophages express surface markers such as CD86 and secrete pro-inflammatory mediators (TNF- α , IL-1 β , and nitric oxide produced via iNOS). Although essential for host defense against pathogens and tumors, in sterile inflammation, they can cause collateral tissue damage. In contrast, M2 macrophages are characterized by receptors such as CD163 and CD200R, and by the production of anti-inflammatory cytokines (IL-10 and TGF- β), which promote wound healing and tissue remodeling. However, persistent or dysregulated M2 activity has been implicated in fibrosis and tumor progression.¹¹

In RE, macrophages exhibit spatiotemporal dynamics that are pivotal in the transition from acute injury to chronic fibrosis. Under homeostatic conditions, intestinal macrophages primarily reside in the villi beneath the epithelium. Following irradiation, a distinct migratory pattern emerges: by day 3, macrophages begin relocating from villi to crypts; their numbers peak around regenerating crypts by day 6; and by day 30, they return to baseline villous localization.¹² Functionally, M1-type macrophages predominate in the acute phase, exacerbating mucosal injury by releasing pro-inflammatory mediators (eg., IFN- γ , IL-6, IL-1 β , and TNF- α), thereby amplifying the inflammatory cascade. Subsequently, the repair phase is dominated by M2-type macrophages, which coordinate restoration of the mucosal barrier, support antimicrobial defenses, and help prevent post-radiation infection.¹³ Macrophages are also major sources of enzymes involved in extracellular matrix turnover. Prolonged M1 activity can therefore promote pathological sequelae, including fibrosis and vascular sclerosis, before the onset of M2-dominated repair. This duality highlights the double-edged role of macrophages in RE: M1-mediated debris clearance is necessary but may sustain injurious inflammation, whereas M2-mediated healing can inadvertently promote fibrotic remodeling if unregulated.

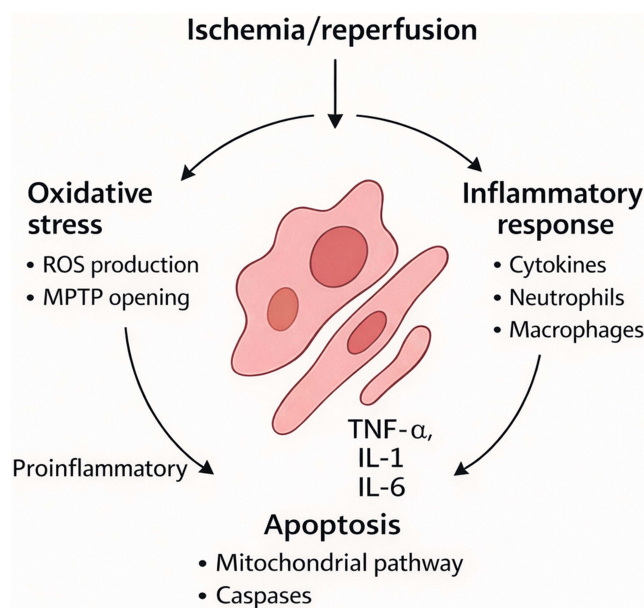


Figure 1 Macrophage polarization. This diagram illustrates the two primary macrophage activation states. Classically activated M1 macrophages, stimulated by agents such as LPS or IFN- γ , express the surface marker CD86 and produce pro-inflammatory cytokines, such as TNF- α , IL-6, and IL-1 β , which act to amplify tissue inflammation. Alternatively activated M2 macrophages, stimulated by IL-4 or IL-13, express markers like CD163 and CD200R and secrete anti-inflammatory mediators, such as IL-10 and TGF- β , which facilitate tissue repair. In RE, an initial M1-dominant response helps clear damaged cells but also exacerbates mucosal injury; a subsequent M2 response aids regeneration but can contribute to fibrosis if excessive or dysregulated.

Given these dynamics, modulating macrophage polarization is a rational therapeutic strategy for RE. Shifting macrophages from an M1- to an M2-like state may help interrupt the cycle of inflammation and tissue injury. Consistent with this idea, agents that modulate macrophage phenotype have shown efficacy in experimental colitis. Notably, PPAR γ signaling has emerged as an endogenous switch that favors M2 polarization.¹⁴ The next section examines how PPAR receptors regulate these phenotypes.

PPAR Signaling in Macrophage Function

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors in the nuclear receptor family. They comprise three isoforms, PPAR α , PPAR β/δ , and PPAR γ , each encoded by a distinct gene and exhibiting unique tissue distributions. All PPARs share a modular structure, including an N-terminal ligand-independent activation function (AF-1), a highly conserved DNA-binding domain (DBD containing zinc fingers), a hinge region, and a C-terminal ligand-binding domain (LBD). In the canonical mechanism, ligand binding promotes heterodimerization of PPARs with retinoid X receptors (RXRs), enabling the complex to bind PPAR response elements (PPREs) in the promoters of target genes.¹⁵ This interaction activates transcriptional programs involved in lipid metabolism, glucose homeostasis, cell proliferation, and inflammation.¹⁶

PPAR function is regulated at multiple levels (Figure 2). Most prominently, ligand binding induces conformational changes that reshape interactions with co-activators and corepressors. In addition, PPAR activity is modulated by post-translational modifications (PTMs), including phosphorylation, SUMOylation, ubiquitination, and acetylation, with subtype-specific PTM patterns.

For PPAR α , phosphorylation has been reported at serine residues 12, 21, 179, and 230. Phosphorylation at Ser12 and Ser21, mediated by mitogen-activated protein kinase (MAPK), enhances AF-1 activity, whereas phosphorylation at Ser179 and Ser230, mediated by protein kinase C (PKC), reduces NCoR recruitment and thereby increases PPAR α activity. In contrast, SUMOylation of PPAR α occurs at lysine residues 185 and 385, selectively recruiting NCoR to inhibit its transcriptional activity.¹⁷ Furthermore, the E3 ubiquitin ligase Mouse Double Minute 2 Homolog (MDM2) regulates PPAR α stability by promoting its ubiquitination and degradation, whereas disruption of the MDM2–PPAR α interaction stabilizes PPAR α .¹⁸

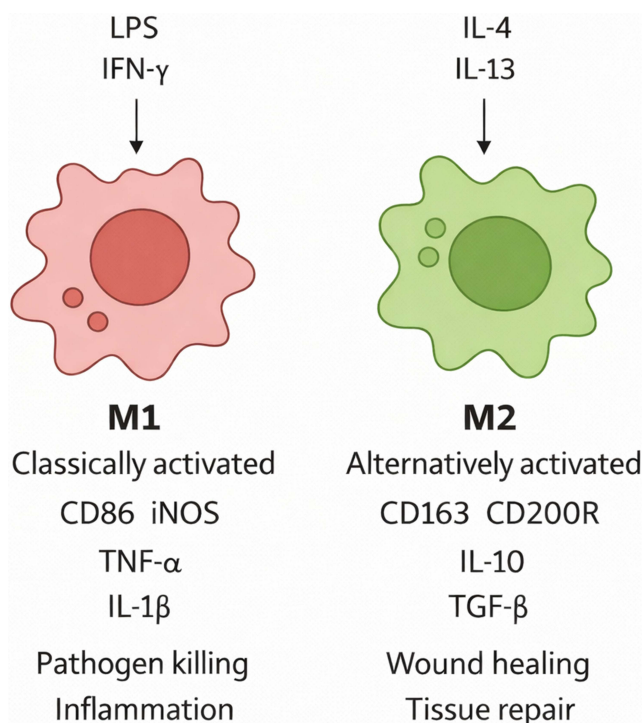


Figure 2 PPAR structure and mechanism. Schematic of PPAR isoforms (α , β/δ , γ) with their DNA-binding (DBD) and ligand-binding (LBD) domains, and illustration of two primary transcriptional regulatory modes. Upon ligand binding, PPAR–RXR heterodimers bind to PPREs and recruit co-activator complexes to initiate gene transcription (trans-activation). PPARs can also inhibit inflammatory gene expression by interfering with pro-inflammatory transcription factors, such as NF- κ B/AP-1, by recruiting corepressor complexes to their target promoters (trans-repression).

PPAR γ PTMs exhibit greater diversity and functional consequences. Phosphorylation of PPAR γ plays a crucial role in regulating metabolic homeostasis. Phosphorylation of tyrosine residue 78 significantly suppresses the expression of pro-inflammatory genes in adipocytes and alleviates adipose tissue inflammation.¹⁹ Conversely, CDK5-mediated phosphorylation at serine 273 is linked to abnormal expression of genes like adiponectin and insulin resistance.^{20,21} PKC α -mediated phosphorylation at Thr166 impairs the induction of beige adipocytes within white adipose tissue (WAT).²² This modification has therefore emerged as a therapeutic target: certain PPAR γ ligands with weak transcriptional activity can exert hypoglycemic effects by blocking phosphorylation at Thr166, thereby decoupling metabolic benefits from the classic thiazolidinedione (TZD) adverse effects of weight gain and fluid retention.²³

Furthermore, PPAR γ phosphorylation influences tumor cell proliferation and apoptosis. In the setting of DNA damage, agents such as carboplatin induce phosphorylation of PPAR γ at Ser273, thereby enhancing DNA damage repair. In contrast, non-classical PPAR γ agonist ligands (NALs) inhibit this process and can sensitize tumor cells to chemotherapy.²¹ Phosphorylation of PPAR γ at Ser84 activates the PFKFB4 promoter, increasing expression of this key glycolytic enzyme and thereby promoting glycolysis and proliferation in hepatocellular carcinoma cells.²⁴ This phosphorylation event also enhances proliferation in human HT1080 fibrosarcoma cells and increases resistance to 5-fluorouracil.²⁵ Collectively, these findings suggest that inhibiting site-specific phosphorylation of PPAR γ may be a viable strategy for anticancer drug development.

SUMOylation of PPAR γ , which predominantly occurs at lysine residues within the AF-1 domain, is another key regulatory modification with diverse functional effects. One well-described anti-inflammatory mechanism involves SUMOylation at sites such as K177, which promotes stable association of corepressor complexes (eg., NCoR) at NF- κ B response elements. This interaction potently transrepresses NF- κ B-driven gene expression, reducing pro-inflammatory cytokine production and promoting a shift in macrophages toward an anti-inflammatory phenotype.^{26,27}

However, studies suggest that the role of the K365 site is nuanced. Although it is implicated in this pathway, evidence indicates that it may not be a direct SUMOylation target but instead facilitates ligand-dependent SUMOylation within the

AF-1 domain via the ligand-binding domain (LBD).²⁸ PPAR γ SUMOylation also serves as a pivotal hub linking lipid metabolism regulation to tumor suppression. Work by the Katafuchi group identified SUMOylation at the K107 site of PPAR γ in white adipose tissue (WAT). This modification enhances insulin sensitivity without the weight gain commonly associated with TZDs.²⁸ Furthermore, the antitumor effects of certain TZDs are mechanistically linked to SUMOylation at K107 and K395. This modification triggers a cascade of metabolic alterations, including upregulation of lipid synthesis and fatty acid β -oxidation genes, leading to NADPH depletion, increased mitochondrial reactive oxygen species (ROS), and disruption of cellular redox balance, collectively inhibiting lung cancer cell proliferation.²⁹

The acetylation status of PPAR γ , which is dynamically regulated by opposing acetyltransferase and deacetylase enzymes, profoundly influences its metabolic functions. PPAR γ acetylation promotes the conversion of brown adipose tissue (BAT) to white adipose tissue (WAT) and accelerates the progression of age-related metabolic disorders.³⁰ Conversely, PPAR γ deacetylation reverses these effects, confirming the critical role of this modification.³¹ Moreover, targeted deacetylation at Lys268 and Lys293 enhances insulin sensitivity with efficacy comparable to thiazolidinediones (TZDs), while avoiding some of their typical side effects, thereby identifying a potential molecular target for the treatment of obesity and diabetes.³²

Cellular PPAR γ abundance is predominantly controlled by the ubiquitin–proteasome pathway. This process is mediated by E3 ubiquitin ligases, which can be functionally divided into two classes: pro-degradative and pro-synthetic, that engage distinct domains of PPAR γ . Ultimately, both classes catalyze PPAR γ ubiquitination, promoting proteasomal degradation and suppressing lipogenic activity.^{33,34}

In contrast to PPAR γ , the regulatory landscape of PPAR δ/β is less well characterized. Epidermal growth factor (EGF) stimulates phosphorylation of tyrosine 108 in PPAR δ , thereby recruiting heat shock protein 90 (HSP90) to prevent lysosomal degradation.³⁵ SUMO-specific protease 2 (SEN2) promotes fatty acid oxidation (FAO)-associated gene expression by de-SUMOylating lysine 104 of PPAR δ .³⁶

PPAR γ is the most extensively studied member of the PPAR family and is widely expressed in adipose tissue and the intestinal epithelium, as well as in macrophages and dendritic cells. In macrophages, PPAR γ drives polarization toward an anti-inflammatory phenotype. Macrophages derived from PPAR γ conditional knockout mice exhibit significantly reduced arginase activity, a canonical marker of M2 polarization.³⁷ Mechanistically, ligand-activated PPAR γ suppresses the production of pro-inflammatory cytokines by antagonizing key transcription factors. For example, PPAR γ can directly interact with NF- κ B and AP-1: upon ligand binding, PPAR γ –RXR dimers recruit corepressor complexes to NF- κ B/AP-1 target promoters, thereby mediating transrepression of inflammatory genes. In vitro, treatment of macrophages with PPAR γ agonists inhibits LPS-induced TNF- α and IL-6 expression through this mechanism.³⁸ Similarly, PPAR γ activation suppresses the NLRP3 inflammasome by reducing ROS and thioredoxin-interacting protein (TXNIP), thereby further inhibiting IL-1 β maturation.³⁹ Endogenously, colonic cells synthesize PPAR γ ligands; notably, 13-oxo-ODE (a metabolite of linoleic acid) binds PPAR γ with high affinity in the gut epithelium and exerts anti-inflammatory effects.⁴⁰ Diminished PPAR γ activity has been observed in patients with inflammatory bowel disease (IBD), implicating this pathway in intestinal inflammation.

In contrast, PPAR α and PPAR β/δ also exhibit anti-inflammatory properties that are relevant to intestinal macrophage function and RE pathophysiology. PPAR α , which is highly expressed in the liver, heart, muscle, and immune cells, plays a crucial role in regulating intestinal macrophage phenotypes. Mechanistically, PPAR α suppresses pro-inflammatory cytokine secretion and promotes IL-10 expression by inhibiting the NF- κ B/AP-1 pathway. It also maintains gut microbiota homeostasis, preventing abnormal macrophage activation, ultimately suppressing intestinal inflammation and preserving mucosal immune balance. In PPAR α -deficient mice, intestinal macrophages abnormally secrete elevated levels of IL-1 β , IL-6, and TNF- α , leading to persistent intestinal mucosal inflammation.⁴¹ Moreover, PPAR α 's classical function is to regulate lipid metabolism. Protein-protein interaction (PPI) analysis confirms direct interactions between PPAR α and lipid metabolism-related genes (eg., ACOX1, CPT1A), ensuring energy supply for macrophages within the inflammatory microenvironment and indirectly supporting their function.⁹ For example, fibrates (PPAR α agonists) increase IL-10 and decrease IL-17 in colitis models.⁴²

Similarly, PPAR β/δ , which is broadly expressed, exerts anti-inflammatory effects by modulating the immune-inflammatory pathways directly. Activated PPAR β/δ binds directly to the κ B element region of pro-inflammatory gene promoters (such as TNF α), competitively displacing the NF- κ B p65 subunit bound there and thereby inhibiting transcription of pro-inflammatory genes. Furthermore, PPAR β/δ recruits the co-inhibitory factor BCL6 to further suppress NF- κ B-mediated

transcriptional activation.⁴³ PPAR β/δ agonists can also directly alter the morphological and functional phenotype of human macrophages, inducing IL-4-mediated M2-type anti-inflammatory characteristics while reversing or inhibiting LPS/IFN- γ -induced M1-type pro-inflammatory polarization.⁴³ Pan-PPAR and dual PPAR α/γ agonists are under active investigation. Collectively, PPARs act as molecular rheostats, shifting macrophage gene expression from pro-inflammatory programs toward pro-resolution and repair. These observations provide a strong rationale for targeting PPAR signaling in RE to promote tissue-protective macrophage phenotypes.

PPAR-Targeted Therapeutic Strategies

Given the anti-inflammatory functions of PPAR γ (and, to a lesser extent, PPAR α and PPAR δ), synthetic agonists have been investigated in models of colitis and other GI inflammation. Although the initial injury in RE arises from physical ionizing radiation, the downstream pathological cascade it triggers exhibits substantial histological and molecular similarities to ulcerative colitis (UC) and to chemically induced animal models. This includes depletion of intestinal epithelial stem cells, breakdown of the mucosal barrier due to decreased expressions of tight junction protein, secondary dysregulation of the immune microenvironment (including NF- κ B pathway activation and pro-inflammatory cytokine storms), and gut microbiota dysbiosis.^{44,45} These intestinal diseases exhibit high consistency in the pathophysiological progression of mucosal damage and in treatment endpoints centered on ‘mucosal healing’. Consequently, chemically induced colitis (such as DSS and TNBS) and clinical UC patient cohorts are frequently utilized as valuable translational parallel alternative models. They are widely applied to investigate the pathogenic mechanisms of RE and to screen potential targeted therapeutic interventions.

The thiazolidinedione (TZD) class of drugs, including rosiglitazone and pioglitazone, comprises high-affinity PPAR γ agonists originally developed for diabetes. In experimental colitis models (eg., dextran sodium sulfate or TNBS), TZDs consistently ameliorate mucosal damage, suppress pro-inflammatory cytokines, and improve barrier function.⁴⁶ For example, in *Clostridioides difficile*-infected mice, pioglitazone alleviated colitis symptoms and downregulated TNF- α , IL-6, and other cytokine genes.⁴⁶ In vitro, pioglitazone-treated macrophages exhibit reduced NF- κ B activity.⁴⁷ However, systemic TZDs are associated with significant adverse effects, including fluid retention, weight gain, bone loss, and increased cardiovascular risk.⁴⁸ Pioglitazone has been shown to promote bladder cancer in rodents.⁴⁹ Although no clear carcinogenic risk has been identified in human clinical studies, long-term monitoring is warranted. Meanwhile, the first-generation TZD rosiglitazone has been withdrawn from the market because of severe hepatotoxicity. Such adverse events constrain the clinical utility of TZDs for chronic GI conditions. An innovative strategy to overcome this limitation is site-specific delivery: for instance, AS002 is an oral PPAR γ agonist engineered to act locally in the colon. In preclinical studies, AS002 showed negligible systemic absorption yet upregulated the expression of PPAR γ -responsive genes in the colonic mucosa. In biopsies from patients with ulcerative colitis, AS002 potently induced adipophilin (a PPAR γ target) and reduced TNF- α and IL-1 β levels. In a DSS colitis mouse model, rectal AS002 ameliorated and even reversed inflammation, as evidenced by lower myeloperoxidase and cytokine levels.⁵⁰ Together, these findings indicate that gut-restricted PPAR γ agonism can provide therapeutic benefit while minimizing systemic exposure. Endogenous PPAR γ ligands are primarily derived from host metabolism or the intestinal microbiota and generally exhibit high biocompatibility, low toxicity, and favorable safety profiles. 13-Oxo-ODE and 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂ (15d-PGJ₂) function as endogenous PPAR γ ligands,⁴⁰ activating PPAR γ -mediated anti-inflammatory pathways while potentially avoiding the systemic metabolic side effects associated with thiazolidinediones (TZDs).⁵¹ Butyrate, an endogenous PPAR γ ligand produced by gut bacteria, mitigates intestinal inflammation by suppressing the dysbiotic expansion of *Enterobacteriaceae*, suggesting a potential therapeutic approach for inflammatory bowel diseases.⁵² Recent preclinical work has also identified natural PPAR γ modulators. Ellagic acid activated the RXR β -PPAR γ pathway in a CT26 tumor-induced cachexia mouse model, supporting its relevance as a natural PPAR γ modulator.⁵³

PPAR α agonists (fibrates) have also shown anti-inflammatory potential. Fenofibrate and WY-14643, for example, enhanced IL-10 production and expanded regulatory T cells in colitis models.⁵⁴ In one mouse colitis study, fenofibrate improved mucosal healing. However, fibrates can elevate plasma homocysteine and creatinine levels, and their gut-specific effects are less well characterized.⁵⁵ Endogenous PPAR α agonists primarily include fatty acids and their derivatives, endocannabinoids, and specific arachidonic acid metabolites. Palmitoylethanolamide (PEA) significantly

attenuates colitis symptoms in mice by activating PPAR α , thereby inhibiting the expression of pro-inflammatory markers such as iNOS and COX-2.⁵⁶ PEA occurs naturally in egg yolks and peanuts. Given its favorable safety profile, low incidence of side effects, and minimal risk of dependence or toxicity, PEA has been used clinically as a dietary supplement.⁵⁷

Dual PPAR agonists and pan-PPAR modulators represent another therapeutic avenue, as coactivation of multiple PPARs may synergize anti-inflammatory and metabolic effects. For example, the PPAR α/γ agonist saroglitazar has demonstrated antifibrotic properties in intestinal fibroblasts.^{58,59} The PPAR α/δ agonist elafibranor (ELA) inhibits M1 polarization signals (TLR4, IFN γ) in the ileum while stimulating IL-10/STAT3 signaling to promote M2 polarization, thereby restoring intestinal barrier integrity in DSS-induced colitis mice.⁶⁰ Conjugated linoleic acid (CLA), a natural PPAR ligand, ameliorates colitis by activating PPAR γ and PPAR δ .⁶¹ Punicic acid (PUA) is another natural dual agonist of PPAR δ that simultaneously activates PPAR γ . It inhibits the secretion of pro-inflammatory factors by macrophages while promoting intestinal mucosal repair.⁶²

In summary, both synthetic and endogenous PPAR agonists demonstrate therapeutic potential in experimental intestinal inflammation. As shown in Table 1, synthetic agonists, including TZDs, fibrates, gut-restricted PPAR γ agonists, and dual PPAR modulators, can attenuate mucosal injury, suppress inflammatory signaling, and promote repair. However, their systemic adverse effects remain a major obstacle to translation.^{60,63–73} As shown in Table 2, endogenous and naturally derived agonists generally provide a safer and more intestine-compatible alternative, with favorable anti-inflammatory activity but variable potency and limited translational validation.^{62,69,74–78} Together, these findings suggest that PPAR-targeted therapy is promising for RE. Nevertheless, its clinical application will likely depend on strategies that deliver these agents specifically to the gut and macrophages while minimizing systemic toxicity. Nanoparticle-based platforms may provide such a solution through targeted and controlled drug delivery.

Nanoparticle Delivery Systems for RE

Nanotechnology offers a versatile platform for the precise delivery of therapeutics to diseased tissue. In the context of RE, ideal nanocarriers should (1) tolerate the harsh gastrointestinal milieu, (2) release their therapeutic cargo within

Table 1 Comparison of the Therapeutic Efficacy and Safety of Synthetic PPAR Receptor Agonists

| Subtype Selectivity | Representative Agents | Preclinical Efficacy in Colitis/ Intestinal Inflammation Models | Systemic Toxicity & Safety | Authors |
|----------------------|--|---|--|---|
| PPAR γ | Thiazolidinediones (Rosiglitazone, Pioglitazone, Troglitazone) | Attenuates mucosal damage, reduces pro-inflammatory cytokines (TNF- α , IL-6), decreases macrophage NF- κ B activity, and improves intestinal barrier function. | Fluid retention, weight gain, bone loss. Increased cardiovascular risk (rosiglitazone), bladder cancer risk in rodents (pioglitazone), and severe hepatotoxicity (troglitazone). | Zhang J, et al ⁶³ Noori M, et al ⁶⁴ Vanasse A, et al ⁶⁵ Tang H, et al ⁶⁶ |
| | Gut-Restricted Agonists (AS002) | Upregulates PPAR γ -responsive genes locally, prevents/reverses inflammation, and reduces myeloperoxidase (MPO) and cytokine levels. | Negligible systemic circulation and avoiding traditional TZD-associated side effects. | Da Silva S, et al ⁶⁷ |
| PPAR α | Fibrates (Fenofibrate, WY-14643) | Promotes IL-10 production, regulatory T cell (Treg) differentiation, and mucosal healing. | Elevate plasma homocysteine and creatinine levels. | Cuzzocrea S, et al ⁶⁸ Esposito G, et al ⁶⁹ |
| PPAR α/γ | Saroglitazar | Exhibits anti-fibrotic effects. | Mild gastrointestinal symptoms, headache, and fatigue. | Jain MR, et al ⁷⁰ Rodriguez-Gutierrez R, et al ⁷¹ |
| PPAR β/δ | GW0742 | Alleviates ischemia-reperfusion injury | Promotes tumor growth and angiogenesis. | Di Paola R, et al ⁷² Faulkner A, et al ⁷³ |
| PPAR α/δ | Elafibranor | Promotes M2 polarization and restores barrier integrity. | Mild gastrointestinal symptoms and musculoskeletal symptoms such as arthralgia and myalgia. | Hakeem AN, et al ⁶⁰ |

Table 2 Comparison of the Therapeutic Efficacy and Safety of Endogenous PPAR Receptor Agonists

| Subtype Selectivity | Representative Agents | Preclinical Efficacy in Colitis/Intestinal Inflammation Models | Systemic Toxicity & Safety Profile | Authors |
|----------------------|--|--|---|---|
| PPAR γ | 15d-PG $_2$, 13-Oxo-ODE, Butyrate, Punicic acid, α -Eleostearic acid | Reduces pro-inflammatory cytokines (TNF- α , IL-6), decreases macrophage NF- κ B activity. Inhibiting the dysbiotic expansion of Enterobacteriaceae (Butyrate) | High intestinal compatibility, low toxicity, no systemic metabolic side effects of TZDs | Meerts IATM, et al ⁷⁴ Byndloss MX, et al ⁷⁵ Takagi T, et al ⁷⁶ Altmann R, et al ⁷⁷ |
| PPAR α | Endocannabinoid-like Compounds (Palmitoylethanolamide) | Inhibits pro-inflammatory markers (iNOS, COX2) | Extremely rare side effects, no dependency or toxicity | Petrosino S, et al ⁷⁸ Esposito G, et al ⁶⁹ |
| PPAR γ/δ | Conjugated linoleic acid | Suppresses NF- κ B signaling, decreases pro-inflammatory cytokines, and upregulates anti-inflammatory molecules such as TFF3 | Good overall tolerability and low toxicity | Bassaganya-Riera J, et al ⁶² |

inflamed intestinal mucosa, and (3) be selectively internalized by macrophages. Advances in materials science have produced diverse nanoparticle (NP) architectures capable of meeting these objectives.⁷⁹ Nanoparticles can encapsulate small-molecule drugs, biologics, or nucleic acids, protecting them from degradation and enabling controlled release. They can also be conjugated with targeting ligands or engineered to release cargo in response to specific biological stimuli.

Lipid-based systems are widely used for their biocompatibility and their ability to fuse with cell membranes.⁸⁰ Polymeric NPs enable tunable degradation rates and drug-release profiles.⁸¹ Inorganic nanocarriers, such as mesoporous silica, iron oxide, or gold NPs, provide robust scaffolds with versatile surface chemistry.⁸² Bio-derived carriers, including exosomes and cell membrane-coated NPs, exploit natural vesicles to evade the immune system. For example, intestinal macrophages can be targeted by coating NPs with macrophage cell membranes, leveraging homotypic interactions.⁸³

Key advantages of nanocarriers in RE include improved drug stability in the GI tract and the potential for colon targeting. Oral nanoparticles can be engineered to withstand gastric acidity and enzymatic degradation. Once in the colon, inflammation can increase vascular permeability and promote local retention of nanomaterials. A recent review highlights that nanoparticle-based oral systems can enhance the bioavailability and sustained retention of therapeutics in the colon, thereby improving outcomes in ulcerative colitis.⁸⁴ By confining the drug to the site of pathology, NPs diminish systemic side effects and permit lower dosages.

To preferentially engage macrophages, nanoparticle surfaces can be decorated with ligands that bind cognate receptors expressed on macrophages. Hyaluronic acid (HA) is one such ligand: it binds CD44, which is highly expressed on activated macrophages in inflamed tissue. A 2024 study engineered rapamycin-loaded liposomes incorporating HA and a ROS-cleavable linker. These ROS-responsive, HA-coated liposomes (Ra@TH) remained inert in healthy tissue but released rapamycin in response to elevated ROS in inflamed mucosa. In vitro and in mouse colitis models, Ra@TH preferentially delivered the drug to CD44+ cells, induced autophagy, and inhibited NF- κ B activation.⁸⁵ This strategy illustrates how coupling inflammatory cues (ROS) with cell-surface targeting (HA) can localize therapy to macrophages in the injured gut.

Zhao et al⁸⁶ synthesized lactoferrin-modified liposomes (LF-lipo). Because activated colonic macrophages over-express low-density lipoprotein receptor-related protein-1 (LRP-1), and lactoferrin binds this receptor with high affinity, these liposomes can be actively guided to their targets. Liu et al⁸⁷ used PEGylated lipids conjugated to the S2P peptide to recognize the Stabilin-2 (STAB2) receptor on M1 macrophages, thereby achieving selective targeting. Huang et al⁸⁸ developed an oral nanomedicine with a surface coating of low-molecular-weight heparin (LMWH). LMWH selectively binds integrin α M, which is abundant on macrophages within inflamed gut tissue. Both cell-based and in vivo experiments confirmed this selective binding and the associated therapeutic benefit.

Dextran and mannose are also widely used macrophage-targeting ligands. Macrophages readily internalize dextran-coated NPs via scavenger receptors. For example, Jain et al⁸⁹ formulated dextran-based carriers encapsulating IL-10;

these particles were efficiently taken up by M1 macrophages and reprogrammed them toward an M2 phenotype. Polyethylenimine NPs modified with mannose have likewise been shown to target monocytes/macrophages and promote M1-to-M2 polarization. These approaches could be adapted to deliver PPAR agonists; for instance, a mannose-decorated NP carrying a PPAR γ ligand could preferentially modulate gut macrophages to induce an anti-inflammatory program.

Other targeting strategies include Fc fragments, peptides, or antibodies directed against macrophage markers. The nanoparticle drug delivery platform demonstrates unique advantages in pharmacokinetics and targeted distribution. Compared to conventional free drugs that are rapidly degraded, nanoparticle carriers effectively resist destruction by gastrointestinal digestive fluids and prolong retention time in damaged intestines. Following oral administration, Lip-LF primarily targets and accumulates in the small intestine—a region highly consistent with the key lesion site in radiation-induced intestinal injury (RIII). Cy5 fluorescence labeling and tracking further demonstrate that Lip-LF exhibits a significantly longer retention time in the gastrointestinal tract compared to free LF.⁹⁰ Zhang et al⁹¹ developed a microalgae-nanoparticle integrated system (SP@ASXnano) that exhibits a significantly longer retention time in the gastrointestinal tract than standalone ASXnano, thereby substantially enhancing drug exposure duration at target sites. Importantly, nanocarriers can also passively target macrophages via phagocytosis; in inflamed tissue, these cells avidly internalize particulate material. Uptake efficiency is size-dependent, with diameters of 50–200 nm yielding maximal phagocytic sequestration.⁹² Specific small-molecule polymers can employ the Enhanced Permeability and Retention (EPR) effect to target inflamed tissues by penetrating the inflamed, hyperpermeable vascular walls. Therefore, by carefully optimizing NP properties, one can maximize macrophage specificity while minimizing uptake by other cells.

The radiation enteritis microenvironment exhibits mild acidosis (pH \approx 6.5) and pronounced oxidative stress (elevated H₂O₂). Nanocarriers engineered with pH-sensitive polymers can exploit these cues: the polymers remain stable at physiological pH but selectively solubilize in the acidic, inflamed mucosa, enabling site-specific drug release.⁹³ Similarly, ROS-sensitive linkers can cleave in the presence of elevated ROS, as demonstrated in the RA@TH system. Enzyme-responsive NPs can also be designed to respond to proteases or matrix metalloproteinases that are enriched in RE.

Zhang et al used oxybutylcyclodextrin (OxbCD) to assemble a nanoscale drug-delivery carrier. Markedly elevated H₂O₂ concentrations at sites of colonic inflammation trigger OxbCD hydrolysis, leading to carrier disruption and release of the encapsulated drug. The OxbCD nanomatrix may also mimic catalase activity, conferring H₂O₂-scavenging capacity. This can synergize with the loaded drug to reduce the major ROS species (\bullet O₂⁻, H₂O₂, and \bullet OH), thereby producing anti-inflammatory and antioxidant effects.⁹⁴ Thus, the nanoparticle remains structurally intact during systemic circulation or luminal transit and releases its therapeutic payload only upon encountering inflamed intestinal mucosa; such stimulus-responsive delivery increases local drug concentrations while minimizing systemic exposure.

Beyond the RA@TH (ROS-responsive, hyaluronic acid-coated liposomes loaded with rapamycin) paradigm, additional proof-of-concept systems support the utility of targeted, stimulus-responsive delivery. Polymeric nanoparticles surface-functionalized with cell-penetrating peptides have been used to selectively deliver curcumin to colonic macrophages in experimental colitis, resulting in marked attenuation of disease activity.⁹⁵ Nanoparticles coated with anionic heparin can bind integrins and accumulate in inflamed colonic mucosa, serving as “Trojan horses” for small-molecule drugs. Lipid nanoparticles that mimic high-density lipoprotein (HDL) can deliver PPAR α agonists to macrophages via scavenger receptors.⁹⁶ Iron oxide or cerium oxide NPs have intrinsic antioxidant properties and can both neutralize ROS and shift macrophage polarization.⁹⁶ Moreover, engineered cerium oxide nanoparticles exhibit remarkably selective radioprotective effects. Specifically, they provide substantial protection to normal tissues against radiation damage while offering no protection to tumor cells. Zamyatina et al⁹⁷ and Xiang et al⁹⁸ independently confirmed their highly selective radiosensitizing effects on EMT6/P cells (mouse adenocarcinoma) and on lung metastasis, respectively. Although many of these systems remain at the proof-of-concept stage, they underscore the feasibility of targeting macrophage PPAR pathways in GI inflammation.

Light-mediated therapies, including photothermal therapy (PTT), photodynamic therapy (PDT), and photobiomodulation (PBM), represent an emerging class of stimuli-responsive strategies for RE treatment. Characterized by non-invasiveness and precise temporal and spatial control, this approach has been widely applied in fields such as oncology, inflammation, and tissue repair. Common types include photodynamic therapy (PDT), photothermal therapy (PTT), and photobiomodulation (PBM). In recent years, the anti-inflammatory and tissue-repairing effects of light-mediated therapy in radiation-induced intestinal injury

have garnered significant attention. Such strategies enable precise temporal and spatial activation of nanoparticle delivery systems, thereby enabling targeted regulation of macrophage polarization within the intestinal inflammatory microenvironment following radiotherapy. The site of radiation enteritis features a thick, viscous mucus barrier, making it difficult for conventional nanoparticles to reach macrophage surfaces. The localized thermal effect generated by Transient mild photothermia (TMP; $\approx 42^{\circ}\text{C}$, 10 min) reduces the viscoelasticity of the mucus layer while imparting a “nanomotor”-like mechanical motion to nanoparticles, significantly enhancing penetration efficiency.⁹⁹

The photothermal effect triggers structural changes in the nanocarrier and controlled release of its payload. For example, PBN (Prussian Blue + NO donor SNP) exhibits strong near-infrared (808 nm) absorption. Upon NIR irradiation, it efficiently converts light energy into mild thermal energy (temperature rises to $49\text{--}51.3^{\circ}\text{C}$). This approach avoids the non-specific damage associated with conventional high-temperature PTT while simultaneously breaking the Fe-NO coordination bond within PBN. This controlled release of nitric oxide (NO) promotes intestinal epithelial cell proliferation and migration, directly repairing damaged intestinal mucosa. Additionally, the photothermal effect disrupts the electrostatic cross-linked network of the FU/CS hydrogel, accelerating drug release, increasing drug concentration at the site of inflammation, and enhancing anti-inflammatory effects.¹⁰⁰ Photodynamic therapy further synergistically amplifies PPAR agonist-mediated anti-inflammatory and reparative signals. ROS generated by photodynamic processes modulate signaling pathways such as PI3K/AKT/mTOR, inducing macrophage autophagy and metabolic reprogramming to reshape inflammatory responses.¹⁰¹ He et al¹⁰² developed the orally administered prebiotic-modified nanoplatform CBF@LCP. This platform targets M1 macrophages overexpressing folate receptors at colonic inflammatory sites via folate-mediated delivery. Upon near-infrared light activation, it triggers synergistic photodynamic/photothermal therapy (PDT/PTT) to ablate M1 macrophages, promote polarization toward the M2 phenotype, simultaneously restore gut microbiota balance, and inhibit the PI3K/AKT signaling pathway.

Exosomes, as natural nanocarriers, enable specific targeting of intestinal macrophages without complex artificial modifications, thereby avoiding off-target effects associated with systemic distribution. Under inflammatory pathological conditions, compromised intestinal epithelial barriers and increased local vascular permeability allow exosomes—with their nanoscale dimensions (30–150 nm)—to passively accumulate at diseased mucosal sites via a mechanism analogous to the “Enhanced Permeability and Retention (EPR) effect”. Furthermore, the outer leaflet of the exosome lipid bilayer naturally enriches phosphatidylserine, which serves as a classic “eat-me” signal. This signal is efficiently recognized by scavenger receptors on the surface of locally resident intestinal macrophages, triggering endocytosis. Furthermore, extensively expressed transmembrane proteins (eg., CD9, CD63, CD81) and specific integrins on the exosome surface mediate specific adhesion to extracellular matrix components and cellular receptors within the inflammatory microenvironment.^{103,104} Fluorescent labeling has confirmed their efficient delivery to intestinal tissues via tail vein injection, and colocalization analysis demonstrates their active uptake by intestinal macrophages. Qian et al¹⁰⁵ found that compared with exosomes prepared under normoxic conditions, hypoxia-pretreated adipose-derived mesenchymal stem cell-derived exosomes (HExos) strongly induced macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2. This significantly reduced levels of pro-inflammatory factors such as TNF- α , IL-1 β , and IL-6, increased secretion of anti-inflammatory factors such as IL-10, and simultaneously upregulated M2 markers (Arg1, CD206) and downregulated M1 markers (iNOS). Liu et al¹⁰⁶ extracted endometrial regenerative cell-derived exosomes (ERC-Exos) and demonstrated that SIRT6 within these exosomes directly binds to the NF- κ B p65 subunit, inhibiting the phosphorylation of IKK α/β and p65, blocking NF- κ B inflammatory pathway activation. This induces macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2 types. Both in vivo and in vitro experiments have demonstrated its therapeutic efficacy against intestinal inflammation. Yang’s team developed RSPO1-loaded small extracellular vesicles (evRSPO1) using an innovative approach. Unlike conventional vesicle cargo encapsulation, these engineered vesicles employ a surface-loading mode mediated by heparan sulfate proteoglycans (HSPGs).

Engineered extracellular vesicles (EVs) are emerging not merely as passive natural carriers, but as programmable nanoplatforms whose material architecture, surface display strategy, and loading method directly determine target engagement and regenerative efficacy. In the dual-ligand exosome system reported by Yang et al¹⁰⁷ WNT ligands were actively loaded onto exosomes through donor-cell engineering using the Wntless (WLS) scaffold, whereas RSPO1 was co-displayed on the same vesicle to generate exoWNT3A/RSPO1, thereby enabling synergistic activation of WNT/

β -catenin signaling and downstream crosstalk with the PPAR α pathway. This dual-ligand configuration promoted organoid growth and accelerated tissue repair in acute and chronic injury models.¹⁰⁷ In contrast, the orally deliverable evRSPO1 platform used a surface-loading mechanism mediated by heparan sulfate proteoglycans (HSPGs), allowing active RSPO1 protein to remain functionally exposed on the small extracellular vesicle surface; after oral administration, evRSPO1 activated WNT/ β -catenin signaling in the intestinal crypt stem-cell niche and significantly accelerated regeneration in a radiation-induced intestinal injury model.¹⁰⁸ Together, these studies indicate that the therapeutic performance of engineered EVs depends not only on cargo identity but also on whether bioactive ligands are incorporated by donor-cell engineering, surface tethering, or post-isolation modification, as these choices shape vesicle stability, receptor accessibility, tissue biodistribution, and signaling potency. In the context of radiation enteritis, such engineering strategies are especially attractive because they combine the intrinsic biocompatibility of natural vesicles with the potential to deliver instructive regenerative signals rather than anti-inflammatory drugs alone.

To better illustrate the engineering rationale and therapeutic workflow of these bio-derived nanovesicles, Figure 3 summarizes the major steps involved in donor-cell engineering, vesicle preparation and characterization, delivery, intestinal targeting, and downstream regenerative signaling. A comparative perspective is also informative. Compared with conventional synthetic nanoparticles, engineered EVs offer superior biological compatibility, membrane protein-mediated cellular recognition, and a lower risk of mucosal irritation, which may be advantageous in the irradiated intestine.

A comparative perspective is also informative. Compared with conventional synthetic nanoparticles, engineered EVs offer superior biological compatibility, membrane protein-mediated cellular recognition, and a lower risk of mucosal irritation, which may be advantageous in the irradiated intestine. However, they also pose distinct manufacturing challenges, including batch-to-batch heterogeneity, lower production yields, limited control over ligand density, and the need for standardized potency assays. Mechanistically, exoWNT3A/RSPO1 represents a donor-cell-programmed, dual-ligand signaling vesicle optimized for pathway amplification, whereas evRSPO1 is an orally deliverable, surface-loaded regenerative vesicle optimized for intestinal access and stem-cell activation. These differences suggest that future RE-oriented EV design should explicitly match engineering strategy to therapeutic objective: intravenous systems may

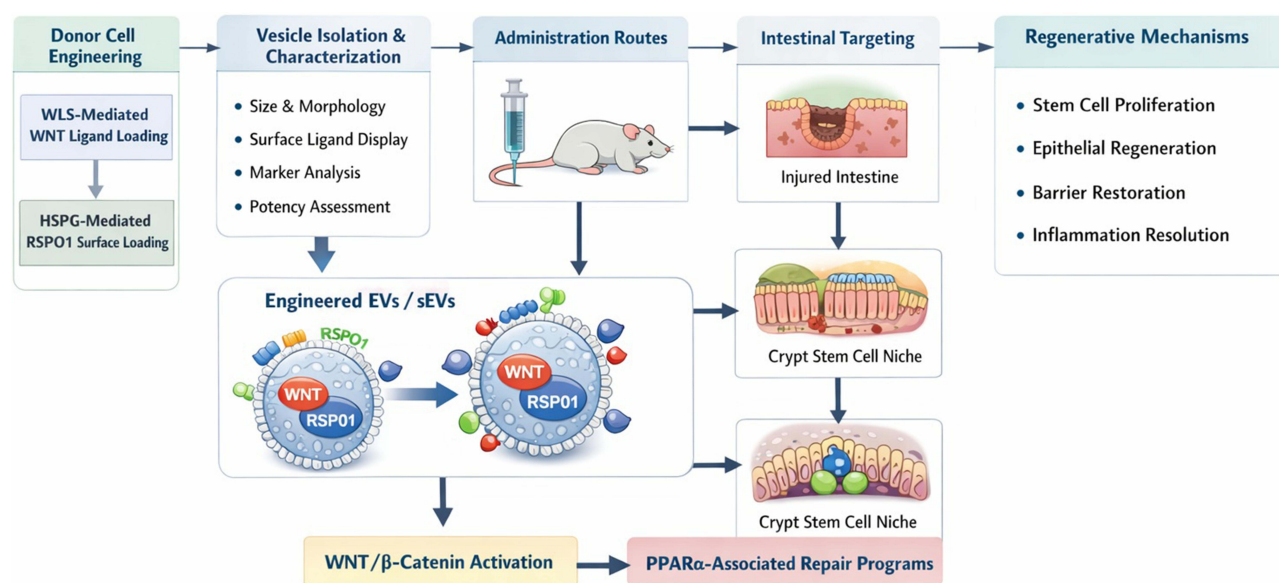


Figure 3 Engineering workflow and therapeutic mechanism of extracellular vesicle-based regenerative nanoplatforams for radiation enteritis. Donor cells are first selected and genetically or biochemically engineered to enable ligand display or cargo loading onto extracellular vesicles (EVs). Two representative strategies are illustrated: (i) WLS-mediated active loading of WNT ligands into engineered exosomes, and (ii) HSPG-mediated surface loading of RSPO1 onto small extracellular vesicles. After isolation and characterization, the engineered vesicles can be administered either intravenously or orally. Intravenously delivered EVs may preferentially accumulate in injured intestinal tissue, whereas orally delivered vesicles can access the intestinal crypt niche after transit through the gastrointestinal tract. Following target engagement, these vesicles activate WNT/ β -catenin signaling and induce downstream PPAR α -associated reparative programs, thereby promoting intestinal stem cell proliferation, epithelial regeneration, barrier restoration, and the resolution of inflammation.

Abbreviations: EV, extracellular vesicle; WLS, Wntless; HSPG, heparan sulfate proteoglycan; RSPO1, R-spondin I; PPAR α , peroxisome proliferator-activated receptor alpha.

be preferable for systemic homing to irradiated bowel, while orally delivered vesicles may be more suitable for direct mucosal and crypt targeting.

From a translational standpoint, several issues deserve closer investigation. First, head-to-head comparisons between engineered EVs and synthetic nanocarriers should be performed in radiation-specific intestinal injury models to define differences in intestinal retention, macrophage uptake, epithelial repair, and systemic exposure. Second, manufacturing variables—including donor-cell source, ligand-display strategy, purification route, and storage stability—should be standardized, because these parameters are likely to influence EV potency and reproducibility. Third, quantitative pharmacokinetic and biodistribution studies are needed to determine whether orally delivered vesicles primarily act lumenally, crypt-specifically, or after trans-epithelial transport, whereas intravenously delivered vesicles require assessment of spleen/liver sequestration versus injured-intestine homing. Finally, future studies should evaluate whether engineered EVs can be combined with PPAR agonists, antioxidants, or microbiota-modulating interventions to achieve synergistic mucosal repair in RE.

These recent studies indicate that engineered EVs are not merely passive carriers but biologically instructive nanoplatfoms whose preparation strategies and surface architectures directly influence signaling potency and tissue repair. The therapeutic efficacy of engineered EVs depends on both vesicle construction and delivery route, which together determine target accessibility, signaling activation, and regenerative outcome.

To facilitate comparison across these emerging strategies, Table 3 summarizes the major nanoparticle platforms developed for intestinal macrophage targeting, including their material composition, targeting ligands, stimulus-responsive features, representative payloads, and principal therapeutic advantages.^{86,88,109–115} Collectively, these platforms highlight several convergent design principles, namely enhanced accumulation in inflamed intestinal tissue, selective uptake by macrophages, and controlled drug release in response to the local inflammatory microenvironment.

Table 3 Comparison of Nanoparticle Platforms for Intestinal Macrophage Targeting

| Carrier Type | Targeting Strategy | Stimuli Responsiveness | Preclinical Model | Therapeutic Outcome | Authors |
|-------------------------------------|--|---|-------------------|---|---|
| RA@TH (HA-coated liposome) | Targets CD44 on macrophages via HA | ROS-cleavable ketone–thiol linker | DSS mice | Induces autophagy (mTORC1↓), inhibits NF-κB, restores barrier function | Chen Y, et al ¹⁰⁹ Hua Y, et al ¹¹⁰ |
| LF-lipo (lactoferrin liposome) | Targets LRP-1 on activated macrophages | Passive targeting | DSS mice | Reduces pro-inflammatory cytokines/ROS, suppresses NF-κB and NLRP3, and ameliorates colitis | Zhao Y, et al ⁸⁶ |
| LNT/BUD-NP (lentinan nanoparticle) | Targets macrophages via Dectin-1 receptor | Passive targeting | DSS mice | Inhibits TLR4/MyD88/NF-κB and reduces inflammation | Lin M, et al ¹¹¹ |
| Ce-Cur@MCS (mannose-CS NP) | Targets mannose receptors on macrophages | Antioxidant (nanozyme) activity | DSS mice | Scavenges ROS, shifts macrophages M1→M2, inhibits ferroptosis; greatly alleviates colitis | Yang J, et al ¹¹² |
| OPNs@LMWH (polylysine NP) | Targets integrin α _M (CD11b) on macrophages | Oxidation-sensitive polymer core | DSS mice | Scavenges ROS, inhibits inflammatory signaling, restores redox balance, and improves colitis | Huang L, et al ⁸⁸ |
| Tp/OxβCD NP (cyclodextrin NP) | Passive targeting via size/eEPR | H ₂ O ₂ -cleavable β-cyclodextrin | DSS mice | H ₂ O ₂ -triggered Tempol release; significantly suppresses colitis symptoms and pro-inflammatory mediators | Zhang Q, et al ¹¹³ |
| Res-CeO ₂ @HA (ceria NP) | Targets CD44 on macrophages via HA | Catalytic ROS scavenging (nanozyme) | DSS mice | Clears ROS; inhibits M1 and promotes M2 polarization via TLR4/NF-κB modulation; restores immune homeostasis | Wang T, et al ¹¹⁴ |
| Cur/CS/Z NP (zein NP) | Chondroitin sulfate binds macrophages (CD44 ligand) | – | DSS mice | Inhibits NF-κB and multiple pro-inflammatory cytokines (TNF-α, COX-2, IL-6, etc.), markedly alleviating colitis | Liu G, et al ¹¹⁵ |

To further evaluate the translational relevance of these platforms, recent studies have begun to clarify how nanoparticle composition and formulation influence intestinal biodistribution, local retention, and safety in irradiated or inflamed bowel. Recent evidence suggests that radiation-induced intestinal injury may enhance the local accumulation and retention of nanocarriers in the gut. For example, orally administered lactoferrin-loaded liposomal nanoparticles displayed markedly prolonged intestinal residence compared with free lactoferrin; at 120 min after administration, the liposomal formulation remained predominantly in the jejunum, whereas free lactoferrin had largely transited to the cecum and colon.⁹⁰ Likewise, intravenously injected mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) preferentially accumulated in irradiated intestines in a dose-dependent manner, with significantly stronger fluorescence signals detected in the intestines of mice exposed to 8–15 Gy abdominal irradiation than in non-irradiated controls.¹¹⁶ These findings indicate that epithelial injury, mucus alteration, and increased permeability after irradiation may create a microenvironment that facilitates nanoparticle adhesion and retention. However, despite encouraging biodistribution data, no nanoparticle-based therapy has yet entered clinical trials specifically for inflammatory bowel disease (IBD) or radiation enteritis (RE), underscoring the persistent translational gap between preclinical proof-of-concept studies and clinical application.¹¹⁷ In addition, safety profiles differ substantially across material classes. Lipid-based formulations generally exhibit favorable gastrointestinal biocompatibility; repeated oral administration of lactoferrin-loaded liposomes did not induce histopathological abnormalities in major organs in mice.⁹⁰ In contrast, certain inorganic nanoparticles, particularly metal- or metal oxide-based systems, may provoke oxidative stress, inflammatory responses, and uncertain long-term tissue accumulation, which are of particular concern in the context of radiation-damaged mucosa.⁹⁴ Collectively, these observations highlight that nanoparticle design for RE should consider not only therapeutic payload delivery but also formulation-dependent pharmacokinetics, intestinal biodistribution, biodegradability, and platform-specific safety.

Despite their promise, nanoparticles face several obstacles. In the bloodstream, proteins can adsorb onto NPs, potentially masking targeting ligands and reducing targeting efficiency. Repeated dosing may also induce anti-PEG antibodies, leading to accelerated blood clearance.¹¹⁸ After oral administration, NPs encounter two principal physiological barriers: the viscous mucus layer and rapid gastrointestinal transit.

To address these challenges, investigators are developing (i) mucoadhesive surface coatings that transiently anchor carriers to the epithelium and (ii) nanoparticle-encapsulating microparticles with pH-insensitive shells that dissolve specifically in the colonic lumen, thereby releasing nanoparticles at the intended site of action (Figure 4). Notably, recent clinical trials in IBD indicate that nano-medicine approaches are advancing toward clinical reality.

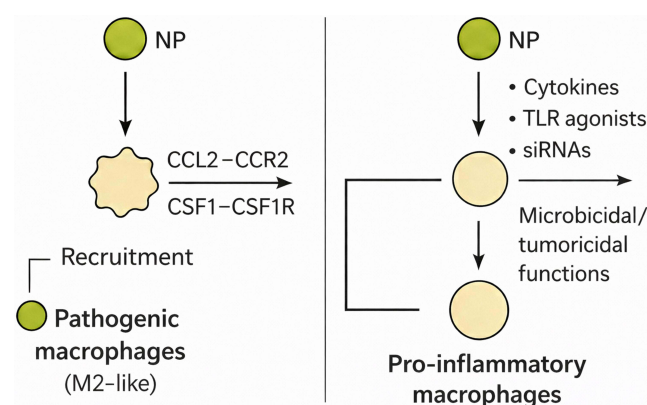


Figure 4 Nanoparticle strategies to modulate macrophages. Schematic illustration of nanoparticle (NP)-mediated modulation of macrophage polarization and function in inflammatory contexts. The diagram depicts two distinct pathways by which NPs influence macrophage behavior. On the left, NPs facilitate the recruitment of pathogenic, M2-like macrophages through the CCL2-CCR2 or CSF-1-CSF1R signaling axes, promoting their migration to sites of inflammation or pathology. On the right, NPs loaded with cytokines, TLR agonists, or siRNAs activate pro-inflammatory macrophages, enhancing their microbicidal and tumoricidal functions. This dual mechanism underscores the versatility of NPs in reprogramming macrophage phenotypes, potentially via PPAR pathways, to mitigate radiation-induced intestinal damage by balancing pro- and anti-inflammatory responses.

Research Frontiers and Emerging Technologies

While engineered nanoparticle delivery systems have significantly advanced targeted modulation of PPAR pathways in macrophage polarization for the management of radiation enteritis (RE), integrating research frontiers such as single-cell omics and microbiomics promises to unravel intricate cellular and microbial dynamics, thereby facilitating the development of next-generation precision therapies.

Single-cell omics analyzes biomolecular information, including genomics, transcriptomics, proteomics, and epigenomics, at the resolution of individual cells. It overcomes key limitations of traditional bulk omics by resolving cellular heterogeneity and delineating the molecular features and functional states of single cells within complex biological systems. In studies of radiation-induced intestinal injury, single-cell omics has provided additional evidence that PPARs modulate radiation enteritis pathology by acting on macrophages. Motevasseli et al¹¹⁹ analyzed macrophage gene-expression matrices using pySCENIC (a Python-based tool for scRNA-seq analysis) and identified PPAR as a key transcription factor governing macrophage phenotypic transitions. Lu et al¹²⁰ used scRNA-seq to show that Ly6c⁺ monocytes give rise to pro-inflammatory and resident macrophages in the context of radiation-induced intestinal injury (RII). They further elucidated a positive feedback loop between macrophages and endothelial cells that exacerbates the inflammatory response, suggesting that macrophages are key targets for mitigating early radiation-induced inflammation. Zhang et al¹¹³ applied gene co-expression network analysis (hdWGCNA) and showed that M1 macrophages stimulate fibroblasts via PPAR, ECM, and interferon- γ signaling pathways, thereby driving excessive ECM deposition. Single-cell omics also enables more precise assessments of therapeutic efficacy by identifying genes highly expressed in inflammatory macrophages and tracking changes in their expression after treatment.

Mennillo et al¹²¹ used scRNA-seq and CITE-seq to compare the expression of TIMP1, SOD2, TYMP, C15orf48, and CD63 in MNP from healthy controls (HC), patients with ulcerative colitis (UC), and patients with treated UC. This analysis supported the efficacy of vedolizumab (VDZ) in controlling intestinal inflammation.

In radiation enteritis, the intestinal microbiota undergoes dysbiosis: taxonomic diversity contracts, and community structure shifts toward opportunistic lineages. Integrated 16S rRNA profiling, shotgun metagenomics, transcriptomics, and metabolomics indicate that pathobionts—particularly Actinobacteria and Proteobacteria—expand at the expense of protective commensals, exemplified by a marked decline in Bacteroides.^{122,123} Nepelska et al¹²⁴ reported that most Actinobacteria strains elicit moderate or no PPAR γ activation and may even indirectly reduce PPAR γ levels. Conversely, certain Bacteroidetes strains activate PPAR γ through ERK1/2-mediated phosphorylation cascades. Thus, the radiation-enteritis-associated perturbation of the gut microbiome converges with PPAR-dependent regulatory circuits. This congruence implies that dysbiosis partly fuels disease pathogenesis by suppressing PPAR γ signalling. Conversely, pharmacological or endogenous activation of PPAR isoforms, exemplified by oleoylethanolamine (OEA), a high-affinity PPAR- α agonist, restructures the microbial community toward a probiotic-rich profile, thereby reinforcing the epithelial barrier and attenuating mucosal inflammation. This reciprocal regulation between gut microbiota and PPARs provides a microbiological basis for developing PPAR-targeted nanomedicines.¹²⁵

In summary, nanocarriers enable precise localization of anti-inflammatory drugs to intestinal macrophages. By directing PPAR agonists to the right cells at the right time, these systems aim to maximize therapeutic benefit while minimizing adverse effects. The next generation of RE therapies will likely integrate immunology, lipid signaling, and nanotechnology to advance truly personalized medicine.

Conclusion

Radiation enteritis remains a significant unmet clinical need, and targeted therapies are still lacking. As reviewed above, macrophages play a central role in RE pathogenesis, and PPAR signaling is a key regulator of macrophage function. Activating PPAR γ (and, to some extent, PPAR α/δ) can shift macrophages away from pro-inflammatory programs and promote mucosal repair. Preclinical evidence consistently supports the efficacy of PPAR agonists in suppressing gastrointestinal inflammation. However, clinical translation will depend on minimizing systemic off-target toxicity and achieving site-restricted delivery to diseased mucosa.

Nano-medicine offers tools to address these challenges. Advances in nanoparticle engineering have enabled the development of carriers that target the injured gut and deliver PPAR modulators to macrophages. Recent studies illustrate this concept: ROS-sensitive, HA-targeted rapamycin-loaded liposomes and mannose-directed IL-10 nanoparticles both repolarize macrophages at sites of inflammation.

Analogous carriers can be loaded with PPAR agonists, mRNA, or gene editors; a single nanoparticle that both inhibits NF- κ B and activates PPAR γ could elicit a synergistic anti-inflammatory response.

However, the clinical translation of nanomedicines is hindered by the complexity of biological systems, unpredictable *in vivo* pharmacokinetics, and reliance on traditional, iterative development workflows. Advances in artificial intelligence (AI) are catalyzing a paradigm shift in nano-medicine research and development, moving from empirically guided (“experience-driven”) to computationally powered (“data-driven”) methodologies. By integrating multi-omics datasets, coupling CRISPR-based screening with machine learning, and analyzing single-cell data from inflammatory niches, AI can predict nanocarrier binding affinities for specific cellular markers. This capability streamlines target identification and supports the rational design of targeted formulations.¹²⁶

AI also accelerates nanoparticle design and synthesis. Through *in silico* simulation of intracellular nanocarrier trafficking, AI models can predict stimulus-dependent release kinetics, facilitating the development of smart, stimuli-responsive delivery systems.¹²⁷ In addition, by analyzing preclinical data, AI tools can forecast nanocarrier biodistribution, targeting efficiency, and potential toxicities. This addresses the persistent challenge of unpredictable nano-drug pharmacokinetics and may substantially reduce the time and cost of *in vivo* experimentation.¹²⁸

Looking ahead, several areas warrant attention. First, additional *in vivo* studies in RE models are needed to evaluate these approaches. Most available data come from chemically induced colitis or infection models; radiation-specific studies are required to determine whether macrophage-targeting nanotherapies can prevent long-term fibrosis. Second, the safety and integrity of nanocarriers must be established. Immune clearance, off-target uptake, and the potential immunogenicity of novel materials require careful assessment. Third, clinical translation would benefit from biomarkers that identify patients most likely to respond to PPAR-targeted interventions. Finally, integrating nano-medicine with existing therapies may provide multipronged protection.

In conclusion, targeting macrophage PPAR signaling via precision nanodelivery holds substantial promise for improving outcomes in radiation enteritis. By leveraging expanding knowledge of inflammatory biology and nanotechnology, the field can move toward therapies that restore irradiated intestinal tissue while minimizing systemic side effects. Cross-disciplinary research will be essential to translate these strategies from the bench to the bedside.

Abbreviations

AF-1, activation function-1; AI, artificial intelligence; AP-1, activator protein-1; BAT, brown adipose tissue; C15orf48, chromosome 15 open reading frame 48; CD, cluster of differentiation; CDK, cyclin-dependent kinase; CITE-seq, cellular indexing of transcriptomes and epitopes by sequencing; CLA, conjugated linoleic acid; CRISPR, clustered regularly interspaced short palindromic repeats; DBD, DNA-binding domain; DNA, deoxyribonucleic acid; DSS, dextran sodium sulfate; EGF, epidermal growth factor; ELA, elafibranor; ERK1/2, extracellular signal-regulated kinase 1/2; EPR, enhanced permeability and retention; EVs, extracellular vesicles; FAO, fatty acid oxidation; GI, Gastrointestinal; Gy, gray; HA, hyaluronic acid; HC, healthy controls; HDL, high-density-lipoprotein; hdWGCNA, high-dimensional weighted gene co-expression network analysis; HSP90, heat shock protein 90; IBD, inflammatory bowel disease; IL, interleukin; iNOS, inducible nitric oxide synthase; LBD, ligand-binding domain; LF-lipo, lactoferrin-modified liposomes; LPS, lipopolysaccharide; LRP-1, low-density lipoprotein receptor-related protein-1; LMWH, low-molecular-weight heparin; MAPK, mitogen-activated protein kinase; MDM2, mouse double minute 2 homolog; MNP, mononuclear phagocytes; MPO, myeloperoxidase; NALs, non-classical PPAR γ agonist ligands; NcoR, nuclear corepressor; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family pyrin domain-containing 3; NPs, nanoparticles; OEA, oleoylethanolamine; OxbCD, oxybutylcyclodextrin; PEG, polyethylene glycol; PKC, protein kinase C; PEA, palmitoylethanolamide; PTMs, post-translational modifications; PPAR, peroxisome proliferator-activated receptor; PPREs, peroxisome proliferator-activated receptor response elements; Ra@TH, rapamycin-loaded hyaluronic acid; RE, radiation enteritis; ROS, reactive oxygen species; RT, radiotherapy; RXRs, retinoid X receptors; SENP2, SUMO-specific protease 2; scRNA-seq,

single-cell RNA sequencing; SOD2, superoxide dismutase 2; STAB2, stabilin-2; SUMOylation, small ubiquitin-like modifier modification; TGF- β , transforming growth factor- β ; TIMP1, tissue inhibitor of metalloproteinases 1; TNBS-2,4,6, trinitro-benzenesulfonic acid; TNF- α , tumor necrosis factor- α ; TZD, thiazolidinedione; TXNIP, thioredoxin-interacting protein; TYMP, thymidine phosphorylase; UC, ulcerative colitis; VDZ, vedolizumab; WAT, white adipose tissue; 5-FU, 5-fluorouracil; 13-oxo-ODE, 13-oxo-octadecadienoic acid; 15d-PGJ₂, 15-Deoxy- $\Delta^{12,14}$ -Prostaglandin J₂; 16S rRNA, 16S ribosomal RNA.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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