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Review Article

Exosome-mediated macrophage regulation for inflammatory bowel disease repair: a potential target of gut inflammation

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Abstract: Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a complex condition without a definite cause. During IBD, immune cells such as macrophages release proinflammatory cytokines and chemokines, contributing to intestinal barrier integrity dysfunction. IBD is largely influenced by macrophages, which are classified into subtypes M1 and M2. M1 macrophages have been found to contribute to the development of IBD, whereas M2 macrophages alleviate IBD. Hence, agents that cause increased polarization of the M2 phenotype could help repair IBD. Exosomes, as ubiquitous conveyors of intercellular messages, are involved in immune responses and immune-mediated disease processes. Exosomes and their microRNA (miRNA) from healthy cells have been found to polarize macrophages to M2 to repair IBD due to their anti-inflammatory properties; however, those from inflammatory-driven cells and disease cells promote M1 macrophages to perpetuate IBD. Here, we review the biogenesis, biochemical composition, and sources of exosomes, as well as the roles of exosomes as extracellular vesicles in regulation of macrophages to repair IBD.

Keywords: Exosomes, extracellular vesicles, inflammatory bowel disease, macrophage

Introduction

IBDs are chronic inflammatory gut diseases that include Crohn's disease (CD) and ulcerative colitis (UC) [1], resulting from the interplay of microbial, environmental, immunological, and genetic variables [2]. IBD is becoming more common in Western nations, as its frequency is rising quickly in recently industrialized nations [3]. In the IBD microenvironment, there is the secretion of several proinflammatory cytokines from immune cells, including interferon-gamma (IFN-γ), interleukin-17F (IL-17F), IL-1α, and IL-25 [4].

Macrophages play essential roles in IBD and are the main gatekeeper of intestinal immunological homeostasis [5]; nonetheless, IBD is linked to improper macrophage activation [6, 7]. There is growing evidence that M1 macrophages, which are traditionally activated, predominate M2 macrophages, which are alternately activated and play a part in the development of IBD [8]. Therapeutic substances that have the ability to convert M1 macrophages that promote inflammation into M2 macrophages that inhibit it could, therefore, be helpful for IBD mitigation [8]. Consequently, controlling macrophage polarization is a viable treatment option for IBD [9].

Extracellular vesicles (EVs) are protein and phospholipid structures in which cells constantly discharge, and appear in the form of smaller (30-200 nanometers (nm)) and bigger (micron size) particulates [10]. Although these vesicles are referred to as EVs, the smaller ones are frequently dubbed exosomes [10]. Most live cells produce exosomes, which are lipid bilayer membrane vesicles measuring 30-150 nm with

significant biological roles [11]. Thus, interest in exosomes' potential to stop the onset of autoimmune disorders, including IBD, is growing [11]. Exosomes are abundant in the milieu of inflammation and are released from immune cells (macrophages, neutrophils, and dendritic cells, etc.), mesenchymal stem cells (MSCs), and platelets as intercellular messengers, which contribute to the control of inflammation through the control of gene expression and the release of anti-inflammatory substances [12]. Additionally, MSC-derived exosomes have been found to exhibit therapeutic benefits for IBD by polarizing M1 macrophages into M2 macrophages, reducing inflammatory reactions, and preserving the integrity of the intestinal barrier [13].

In this review, we summarize the biogenesis, biochemical components, sources of exosomes, and the role of exosomes in regulating macrophages to repair IBD. This review will also cover other compounds regulating macrophages and the role of EVs/nanovesicles in modulating macrophages toward IBD mitigation.

Materials and methods

PubMed and Google Scholar databases were utilized to look for journals mostly concerned with exosomes and exosome-like nanovesicles, macrophages, and IBD. Articles were retrieved up to 2023 using keywords, including "exosome, macrophage, and IBD". After entering these keywords into PubMed and Google Scholar, a review process was conducted to ensure the relevance and eligibility of the journals selected.

Exosome and its sources

Exosomes are microscopic, extracellular vesicles that contain proteins, lipids, nucleic acids, and other bioactive materials that are involved in both normal and pathological activities within the body [14] and are present in different bodily fluids, including amniotic fluid [15], blood plasma [16], saliva [17], breast milk [18], serum [17, 19, 20], ascites [21], urine [15], nasal secretions [22], and cerebrospinal fluid [23]. Exosome-like vesicles (ELVs) are crucial for intercellular communication by serving as cellular transfer vehicles for biomolecules, and this distinctive quality justifies their use as bio-inspired medication delivery devices [24]. Exosomes have the ability to change the biological activity of recipient cells by transferring their cargo inside these cells [25].

Exosomes are secreted by a variety of cells, including bone marrow MSCs [26, 27], umbilical cord MSCs [28-33], adipose tissue-derived MSCs [34-37], neutrophils [38], dendritic cells (DCs) [39], amniotic fluid stem cells [40], ginger [41], tumors [42], mast cells [43], plasma platelets [44], T lymphocytes [45], mantle cell lymphoma [46], macrophage (M1) [47, 48], M2 macrophage [49], and bovine colostrum [50]. Exosomes are appealing in biotechnology and biomedical research. After all, they can serve as both therapeutic agents and disease biomarkers because they share components with their parent cells [51]. Therefore, it is necessary to understand the exosome's biogenesis and biochemical makeup to determine the characteristics that cause it to operate as it does.

Biogenesis of exosome

Most mammalian cell types manufacture exosomes and extracellular vesicles encased in membranes that originate in the endosomal space before release [52]. The final content of exosomes is produced as a result of interactions between endosomes, where they first develop, and then transfer into other intracellular vesicles and organelles [53]. Exosomes originate in multivesicular compartments within eukaryotic cells and are released during the fusion of these compartments with the plasma membrane [54]. Through the process of exocytosis, cells produce exosomes, which are then absorbed by target cells and have the ability to transmit biological information across nearby or distant cells [55]. The intraluminal vesicles of multivesicular endosomes (MVEs) are released as exosomes into the extracellular milieu or segregated into lysosomes for cargo destruction [56] (**Figure 1**).

Exosome biogenesis, secretion, and release have generally been demonstrated to be influenced by a number of processes. Insights into the generation and operation of extracellular vesicles may, therefore, be gained from research on the endosomal sorting complex required for transport (ESCRT) machinery [57]; hence, MVB production depends heavily on the

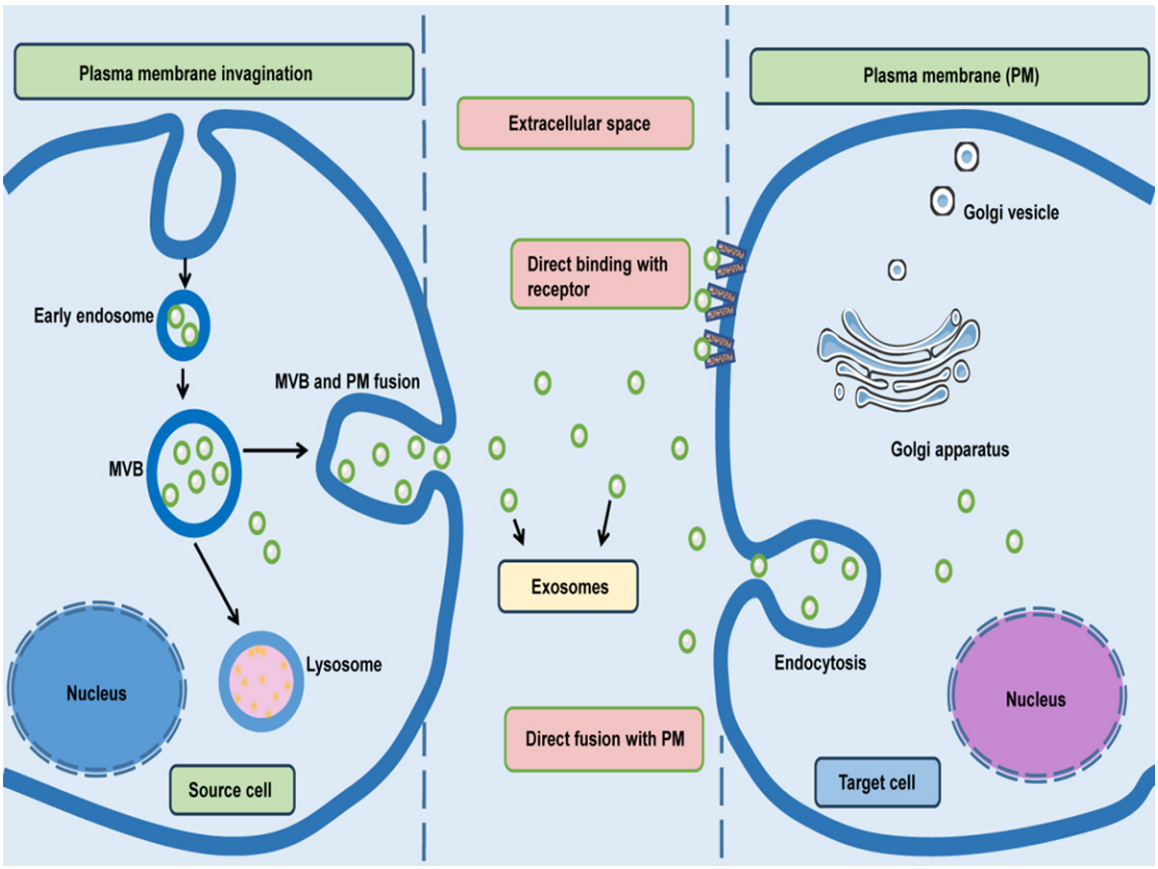

Figure 1. Biogenesis of exosome. Intraluminal vesicles from MVBs release exosomes into the extracellular space. Exosomes move to the target cells via endocytosis, direct fusion, or binding to receptors. Abbreviation: MVBs, multivesicular bodies.

elements of the ESCRT pathway [58]. Nonetheless, it has been demonstrated that gene silencing for two ESCRT-0 elements (*HRS, STAM1*), one of ESCRT-I (*TSG101*), as well as a late-acting component (*VPS4B*), causes regular variations in the secretion of exosomes [59]. The ESCRT machinery is essential for the synthesis of MVEs, allowing cargo choice and intraluminal vesicle (ILV) budding [60]. Additionally, it has been discovered that heparanase modulates the syndecan-syntenin-ALIX pathway, promoting the budding of endosomal membranes and the exosomes' biogenesis by cutting the syndecans' heparan sulfate chains [61]. This mechanism regulates the choice of a particular exosome cargo [61]. Although research has demonstrated that the exosomal protein syntenin promotes the formation of exosomes, uncovered information indicates that the GTPase ADP ribosylation factor 6 (ARF6) and its effector phospholipase D2 (PLD2) also influence exosomes by regulating the budding of ILVs into MVBs [62]. Besides, caveolin-1 (Cav1), which controls the amount of cholesterol in the endosomal compartment/MVBs, controls exosome biogenesis and exosomal protein cargo sorting [63]. Similarly, curcumin activates ceramide synthesis, which increases intracellular ceramide-dihydroceramide concentration, leading to excessive ceramide and a tenfold increase in exosome/microvesicle secretion [64]. Moreover, the mechanistic target of rapamycin complex 1 (mTORC1) has been demonstrated to be a negative regulator of exosome release, which results in a net loss of cellular membrane and protein content [65]. However, ISGylation is a new ubiquitin-like modification that regulates the generation of exosomes [66]. ISGylation of the MVB protein TSG101 causes it to aggregate and degrade, which is enough to prevent exosome secretion [66].

Biochemical components of exosome

Exosomes' molecular makeup reflects the fact that they originated in endosomes as ILVs [67].

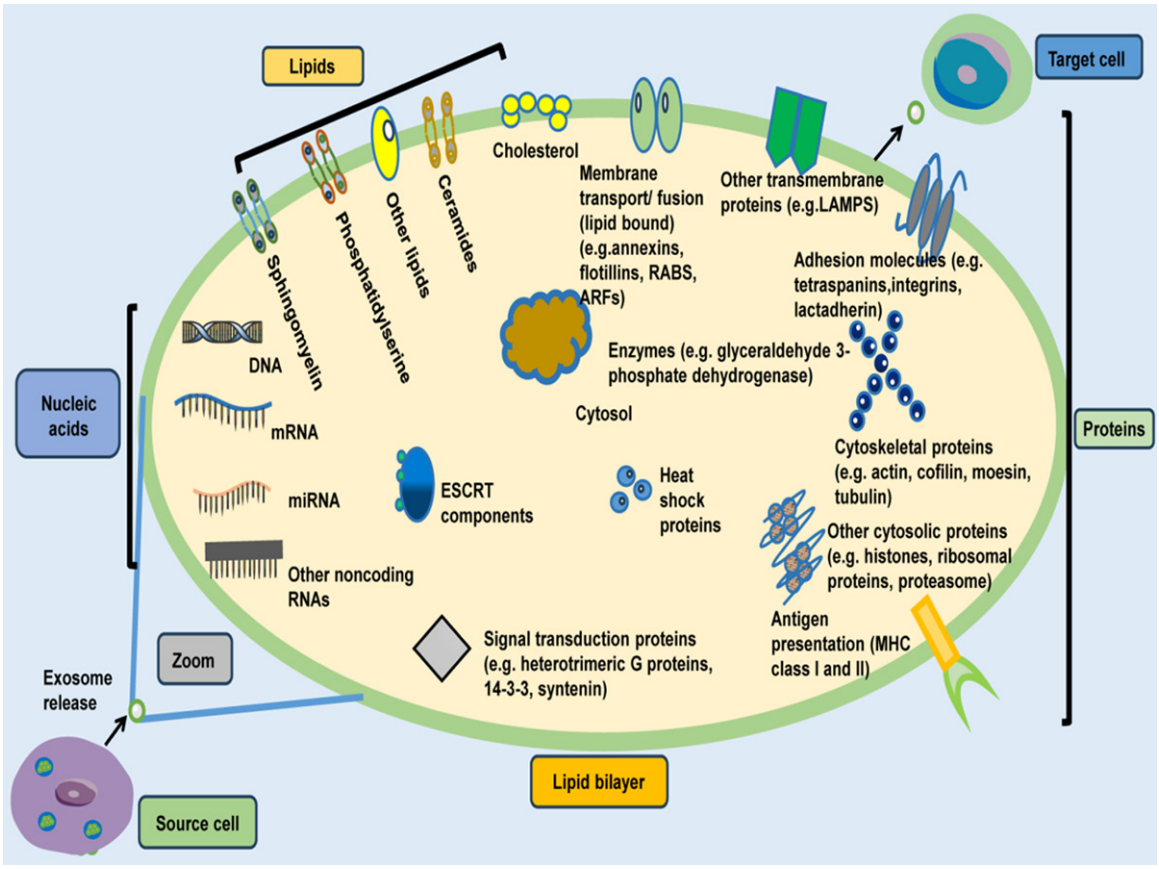

Figure 2. The chemical makeup of exosomes. An exosome (zoomed) is released from a source cell, showing the various biochemical components that are being transferred to the target cell. Abbreviations: ARF, ADP ribosylation factor 6; ESCRT, endosomal sorting complex needed for transport; LAMP, lysosomal associated membrane protein; MHC, major histocompatibility complex; mRNA, messenger RNA; miRNA, microRNA.

Their varied components, which can represent their cell of origin, include nucleic acids, proteins, lipids, amino acids, and metabolites [53]. Moreover, exosomes contain proteins, miRNAs, and messenger RNAs (mRNAs) (exosome shuttle RNA, or esRNA), which may provide a new platform for diagnostics [68]. In general, several of these biochemical components of exosomes have been recognized as indicators for therapeutic and diagnostic approaches to some diseases. This may be because of where they came from biologically and what was in their cargo, which explains why they are helpful as biomarkers for diseases, including IBD. Generally, irrespective of where the exosome is being produced and secreted, it has been shown that exosomes may carry nucleic acids, proteins, and lipids (**Figure 2**). Each element is detailed below.

Proteins

The identification of exosomal marker proteins such as CD24, CD9, annexin-1, and heat shock protein (HSP) 70 has been made, and these proteins also showed the proper buoyant density and antigen orientation [68]. Meanwhile, recent investigations have discovered that MSC exosomal surface marker proteins obtained from the human umbilical cord include CD9, CD63, CD81, HSP 70, Alix, and tumor susceptibility gene 101 (TSG101) without calnexin [29, 30, 69-71]. Additional marker proteins that are frequently seen in the exosomes from β-cells include tetraspanin proteins (CD63, CD82, and CD81), lysosomal associated membrane protein (LAMP)-1 and LAMP-2, intercellular adhesion molecule-1 (ICAM-1), flottilin-1, G-proteins, Alix, TSG101, and Ras-associated binding (Rab) proteins [72]. Meanwhile, TSG101, CD81, and

syntenin have been similarly discovered to have a relative expression in exosome subpopulations [73]. Interestingly, Zhang and colleagues have identified two exosome subpopulations. Large exosome vesicles (Exo-L) were seen with high amounts of proteins such as annexins, charged multivesicular body proteins 1A/2A/4B/5, vacuolar protein-sorting 4 homolog B, DnaJ heat shock protein family (Hsp40) member A1, and myosin IC, while small exosome vesicles (Exo-S) were enriched with flotillin 1, flotillin 2, tweety family member 3, tetraspanin 14, and ESCRT-I subunit VPS37B [74]. These different exosome subpopulations might be a result of different intracellular compartments engaging in exosome loading, according to the existence of genomic DNA (gDNA) [75].

DNA

Exosomes deliver substances with functional activity to aid in intercellular communication [76]. Although the regulatory mechanism is unknown, cancer cells produce exosomes that contain substantial quantities of DNA and can modify the expression of an oncogene in a recipient cell [76]. According to Torralba and team, T cells activate DCs by transferring exosomal DNA, demonstrating a particular function for antigen-dependent interactions in protecting DCs from pathogen infection [77]. Besides, nuclear DNA builds up in the cytoplasm when the secretion of exosomes is inhibited, resulting in the cytoplasmic DNA sensing apparatus being activated [78]. This triggers the innate immune reaction, resulting in a DNA damage response that is dependent on reactive oxygen species (ROS) and thus produces apoptosis, or a cell cycle arrest resembling senescence in normal human cells [78]. According to a report from Takahashi and his team, chromosomal DNA fragments of different lengths can be found in exosomes, demonstrating that exosome secretion keeps cells in a state of equilibrium by eliminating dangerous cytoplasmic DNA [78]. Moreover, murine colitis and active human CD both showed a substantial rise in exosomal double-strand DNA (dsDNA) levels, including mitochondrial (mt) DNA and nuclear genomic DNA (nDNA) [79]. This further corroborates the idea that exosomes may contain DNA.

RNA

Exosomes have a notable enrichment of certain protein and RNA cargoes [80], and exosomes produced by metazoan cells can deliver specific membrane proteins and short RNAs to their target cells to regulate cell migration, development, and metastasis [81]. In different eukaryotes, exosomes have been found to transport RNA cargo, such as short non-coding RNAs and mRNAs, which can change the phenotype of the recipient cell [82].

As components of exosomes, RNAs are transported to exosomes by RNA-binding proteins (RBPs). The synaptotagmin-binding cytoplasmic RNA-interacting protein (Syncrip), also referred to as the heterogeneous nuclear ribonucleoprotein (hnRNP) Q, is a highly conserved RBP that regulates the exosomal partition of a group of miRNAs [83]. Additionally, the RBP Y-box protein I (YBX1) binds to microRNA (miR)-223 and is crucial for the secretion of miRNAs in exosomes by HEK293T cells [81]. The short sequence motif found in miRNAs binds to the RBP fragile X mental retardation 1 (FMR1) and directs the loading of miRNA into exosomes via interactions with elements of the ESCRT pathway [84]. Furthermore, hnRNPA2B1 packages circRNA, specifically circNEIL3, into exosomes in gliomas and transfers it to tumor-associated macrophages that have been infiltrated [85]. Interestingly, without CAVIN1, non-caveolar caveolin-1 (CAV1) promotes hnRPNK localization to MVBs, recruiting miRNAs with the AsUGnA motif and inducing their discharge within exosomes [86].

Exosome components called RNAs are increasingly being used as diagnostic markers in diseases. Extensive research has been done recently on the non-coding RNA (ncRNA) found in exosomes about categorization, localization, and possible use as biomarkers [87]. Exosomal long non-coding RNA (lncRNA) of HDAC4 (LOC85009) reduces docetaxel (DTX) resistance by controlling autophagy-related 5 (ATG5)-induced autophagy via the ubiquitin-specific proteinase 5 (USP5)/upstream transcription factor 1 (USF1) axis, putting LOC-85009 forth as a possible target to overcome DTX resistance in lung adenocarcinoma treatment [88]. Additionally, four brand new trans-

fer (t) RNA-derived small RNAs (tsRNAs) in plasma exosomes, such as tRNA-ValTAC-3, tRNA-GlyTCC-5, tRNA-ValAAC-5, and tRNA-GluCTC-5, have been discovered in individuals with liver cancer, establishing the potential of plasma exosomal tsRNA as a new diagnostic biomarker [89].

Generally, it has been discovered that exosomes contain RNA, lncRNA, miRNA/miR, and tsRNA, some of which may serve as illness diagnostic indicators.

Lipids

Exosome production and release into the external environment depend heavily on lipids and their structural involvement in exosomal membranes [90]. It has been discovered that exosome membranes contain more sphingomyelin, lysophosphatidylcholine, and phosphatidic acid than parental cells do, and interestingly, exosomes have been shown to contain an unusual phospholipid called bis (monoacylglycero) phosphate as a particular lipid indicator for exosomes [91]. Additionally, Llorente and his team found high levels of phosphatidylserine, sphingomyelin, cholesterol, and glycosphingolipids in exosomes [92]. It is also found that glycerolipid, glycerophospholipid, sphingolipid, and glycosphingolipid are contained in the exosomes of prostate cancer cells, even though the class of lipids found in the exosomes with the highest abundance is glycerophospholipid [93]. Similarly, sphingomyelins, phosphatidylinositols, and sulfatides have been found in exosomes of lipids and plasma, but exosome composition has been observed to differ in terms of lipids from plasma in areas of triacylglycerols, diacylglycerols, phosphatidylcholines, and lysophosphatidylcholines [94]. Besides, Elmallah and colleagues found phosphatidylcholine, phosphatidylethanolamine, sphingomyelin, and hexosylceramide (HexCer) to be increased in the exosomes of non-metastatic cells and patients with cancer relative to control cells and healthy donors [95].

Exosomes and exosome-like nanovesicles in macrophage modulation toward IBD repair

Stem/stromal cell-derived exosomes

It is documented that exosome (from human umbilical cord MSCs) therapy in IBD mice reduces macrophage infiltration into the colon tissues [96]. The exosome-treated mice's colon tissues and spleens expressed more IL-10 but less inducible nitric oxide synthase (iNOS) and IL-7 [96]. Additionally, human umbilical cord (huc) MSC-secreted exosomes have been found to relieve colitis by inhibiting casp11/4-induced macrophage pyroptosis [31]. Mechanistically, the exosomes express miR-203a-3p.2 to inhibit casp4-induced macrophage pyroptosis in an inflammatory environment [31]. Another study revealed that hucMSC-derived exosomes suppress the release of IL-1β from mouse peritoneal macrophages even when NOD-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasomes are activated [29]. Moreover, NLRP3, an apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), caspase-1, IL-18, and IL-1β have substantially lower relative expressions in macrophages with hucMSC-derived exosomes [29]. Furthermore, exosomal miR-216a-5p produced by hypoxia-prime adipose-derived stem cells (ASCs) has shown more therapeutic effectiveness than those under normoxia (NExos) in the treatment of experimental colitis by enhancing the M2 macrophage phenotype [97].

According to other studies, intestinal epithelial cells and macrophages can internalize layer-by-layer (LbL)-exosomes from MSC to produce anti-inflammatory and tissue-repair effects [98]. Treatment with LbL-exosome can control inflammation by decreasing M1 macrophages and increasing M2 macrophages [98]. Moreover, Xu and team revealed that tumor necrosis factor α- (TNF-α-) pretreated MSCs generated from human menstrual blood (MenSC)-derived small EVs (MenSCs-sEV$^{TNF-\alpha}$) reduces colonic inflammation, accompanied by the elevation of miR-24-3p in small EVs derived from MenSCs and the polarization of M2 macrophages in the colon [99]. Besides, Cao and colleagues found that bone marrow MSC-derived EVs (BMSC-derived EVs) encourage M2-like macrophage polarization, as evidenced by a rise in the M2 marker CD163 in DSS-induced UC [100]. Also, the systemic administration of exosomes from human bone marrow-derived mesenchymal stromal cells (MSC-Exos) significantly lessens colitis in a variety of IBD models, reduces inflammatory responses, maintains the gut bar-

rier's integrity, and polarizes M2b macrophages [101].

Intestinal epithelial cell (IEC)-derived exosome

The intestinal epithelium is essential for maintaining gut homeostasis because it serves as a physical barrier, a center of coordination for immune defense, and a medium for communication between immune cells and bacteria [102]. IEC exosomes ameliorate IEC damage caused by glucose-oxygen depletion in vitro in addition to the severity of intestinal damage following an intestinal ischemia/reperfusion attack in vivo [103]. Moreover, exosomes from IECs and their cargo, including miRNAs, have been found to control the expression of molecules that promote inflammation in inflammatory gut tissues during sepsis [104]. Appiah and team revealed that proinflammatory cytokines IL-17A and TNF-α messaging are significantly reduced after septic-EV injection into an inflamed gut [105]. Additionally, IEC-derived luminal EVs contain miRNAs that reduce proinflammatory reactions [105]. When an organ is infected or inflamed, macrophages first adopt the M1 phenotype and release TNF-α, IL-1β, IL-23, and IL-12 in response to the stimuli; however, tissue injury may result if the M1 phase lasts longer [106]. Consequently, M2 macrophages release large volumes of transforming growth factor beta (TGF-β) and IL-10 to reduce inflammation, support tissue repair, remodeling, and vasculogenesis, and maintain homeostasis [106]. Hence, M1 macrophages may be activated to release TNF-α; however, IEC exosomes or EVs may activate M2 macrophages to reduce TNF-α as well as damage to the gut.

Macrophage-derived exosome

It's interesting to note that M2 macrophages release exosomes that inhibit IBD. For instance, Deng and team revealed that exosomal miR-590-3p produced by M2 macrophages targets large tumor suppressor homology Ser/Thr kinase 1 (LATS1) and activates Yes-associated protein (YAP)/β-catenin-regulated transcription suppresses cytokines that promote inflammation (including IL-6, TNF-α, and IL-1β), and encourages epithelial regeneration [49]. Moreover, Yang and colleagues showed that M2b macrophage exosomes protect against colitis caused by DSS, primarily controlled by the CC chemokine 1 (CCL1)/CC-chemokine receptor (CCR) 8 pathway, presenting a fresh method for treating IBD [11]. While M2 macrophages release a variety of anti-inflammatory mediators, such as TGF-β, IL-10, CCL1, CCL17, CCL18, and CCL22, M1 macrophages discharge proinflammatory substances such as TNF-α, IL-1α, IL-1β, IL-6, C-X-C motif chemokine ligand 9 (CXCL9), and CXCL10 [107]. Hence, these may imply that M2 exosomes may polarize M2 macrophages to repair IBD while suppressing M1 macrophages.

Other immune cells-derived exosome

Exosomes derived from other immune cells, such as dendritic cells (DCs) and granulocytic myeloid-derived suppressor cells (MDSCs), may play roles in mitigating gut inflammation. It has been found that exosomes generated from immature dendritic cells (IDCs) reduce the early systemic inflammatory response in sepsis by promoting the clearance of apoptotic cells through milk fat globule EGF factor VIII (MFGE8) [108]. Additionally, the TNF-α response elicited by cecal ligation and puncture (CLP) is suppressed by exosomes derived from IDC by 46%; however, in septic rats, mature DC-derived exosomes did not affect TNF-α levels [108]. Similarly, exosomes generated from bone marrow DCs (BMDCs) (containing MFG-E8) increase the removal of apoptotic cells, lower the proinflammatory response, and increase the lifespan of experimental mice with sepsis [109]. The administration of BMDC-derived exosomes decreased TNF-α and IL-6 plasma levels while increasing survival from 44% to 81% [109]. Rats treated with exosomes had peritoneal macrophages that were 2.8 times more capable of phagocytosing apoptotic thymocytes [109]. Again, it has been discovered that the spontaneous improvement of colitis is partially reversed when arginase (Arg)-1 activity in granulocytic (G)-myeloid-derived suppressor cells (MDSC) exosome is inhibited [110]. Arg-1 activity has also been linked to the G-MDSC exosome's capacity to inhibit the delayed-type hypersensitivity (DTH) response, reduce the growth of CD4+ T cells, and suppress the secretion of IFN-γ in vitro [110]. Besides, G-MDSC exosome-treated colitis animals showed reduced TNF-α and IFN-γ blood levels [110], implying that the G-MDSC exosome may activate M2 macrophages to reduce colitis. Surprisingly, one indicator of the M2 anti-inflammatory subgroup is Arg1 [111].

Food-derived exosomes/exosome-like nanovesicles

It has been discovered that turmeric-derived nanovesicles (TNVs) encourage the conversion of M1 phenotype macrophages to M2 macrophages, regulate the gut microbiota, and repair the damaged intestinal epithelial barrier, thus exerting anti-colitis efficacy [112]. Additionally, Kim and colleagues found that ginseng-derived exosome-like nanoparticles (GENs) have the potential to both prevent and reduce inflammatory responses by downregulating proinflammatory cytokines in proinflammatory macrophages and promoting the production of anti-inflammatory macrophages [113]. Spermine, spermidine, and putrescine are polyamines with antioxidant properties, playing a crucial role in biological processes like cell proliferation and differentiation; hence, dietary polyamines have a substantial effect on human health, especially on the development and differentiation of the immune system and intestinal maturation [114]. Interestingly, in the inflammatory colon, spermidine has been shown to downregulate M1 markers while upregulating M2 macrophage markers, as well as decrease the colon's activation of T cells and F4/80 macrophages, mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) phosphorylation, and the production of proinflammatory cytokines [115].

Additionally, Han and his team investigated colostrum-derived exosomes (Col-exo) in DSS-induced colitis and found that Col-exo stimulates macrophages and intestinal epithelial cells and produces an environment that reduces inflammation by successfully eliminating reactive oxygen species and regulating immune cytokine expression [50]. Milk-derived extracellular vesicles (mEVs) enhanced with immunomodulatory proteins and miRNAs prevent the generation of cytokines and the polarization of macrophages toward a proinflammatory phenotype [116]. According to these results, milk and other dairy products include edible nanovesicles (EVs) that have inherent immunomodulatory properties that are good for the gastrointestinal tract [116].

Other exosomes/EVs

It has been found that *Trichinella spiralis*-EVs (*Ts*-EVs) promote the infiltration of alternatively activated (M2) macrophages into the colon and prevent M1 macrophage polarization as a result of their immunomodulatory capabilities [117]. Moreover, the murine counterpart of circRNA SCAR (steatohepatitis-associated circRNA ATP5B regulator), referred to as circRNA mSCAR, declines in septic mice's macrophages, and this is consistent with the M1 polarization being overly intense [118]. However, it has been demonstrated that the exosome-based method of delivering circRNA mSCAR into mitochondria preferentially targets macrophage mitochondria, promoting the M2 subtype of macrophage polarization, reducing systemic inflammation, and reducing septic mouse mortality [118].

Generally, irrespective of the source from which the exosome is being produced, exosomes can activate M2 subtype macrophages, which causes an anti-inflammatory impact that promotes IBD repair (**Figure 3**).

Role of other compounds regulating macrophages towards IBD repair

Wu and colleagues have shown heme supplementation to have a protective impact on the colon tissue microenvironment in mice with DSS-induced colitis via controlling the polarization of macrophages in a heme oxygenase-1 (HO)-dependent and HO-1-independent manner [119]. Moreover, baicalin has been demonstrated to reduce the manifestations of DSS-induced colitis by modifying the polarization of macrophages toward the M2 phenotype [120]. Additionally, lentivirus-mediated short hairpin RNA (shRNA) interference with interferon regulatory factor 5 (IRF5) expression causes a transition in the phenotype of rat peritoneal macrophages from M1 to M2 and decreases IL-1β and TNF-α expression more in depressed colitis rats than in nondepressed colitis rats [121]. Besides, Lu and colleagues found that thalidomide might boost epithelial cells' potential for self-renewal and alter M1/M2 polarization by reducing M1 protein signatures CD86 and CC-chemokine receptor 7 (CCR7) and raising M2 protein signatures CD206 and Arg-1, decreasing the occurrence and development of carcinogenesis linked to colitis compared to mice used as negative controls [122]. Again, lupeol reduces the symptoms of experimental IBD by, at least partially, suppressing M1 and encouraging M2 macrophages [8].

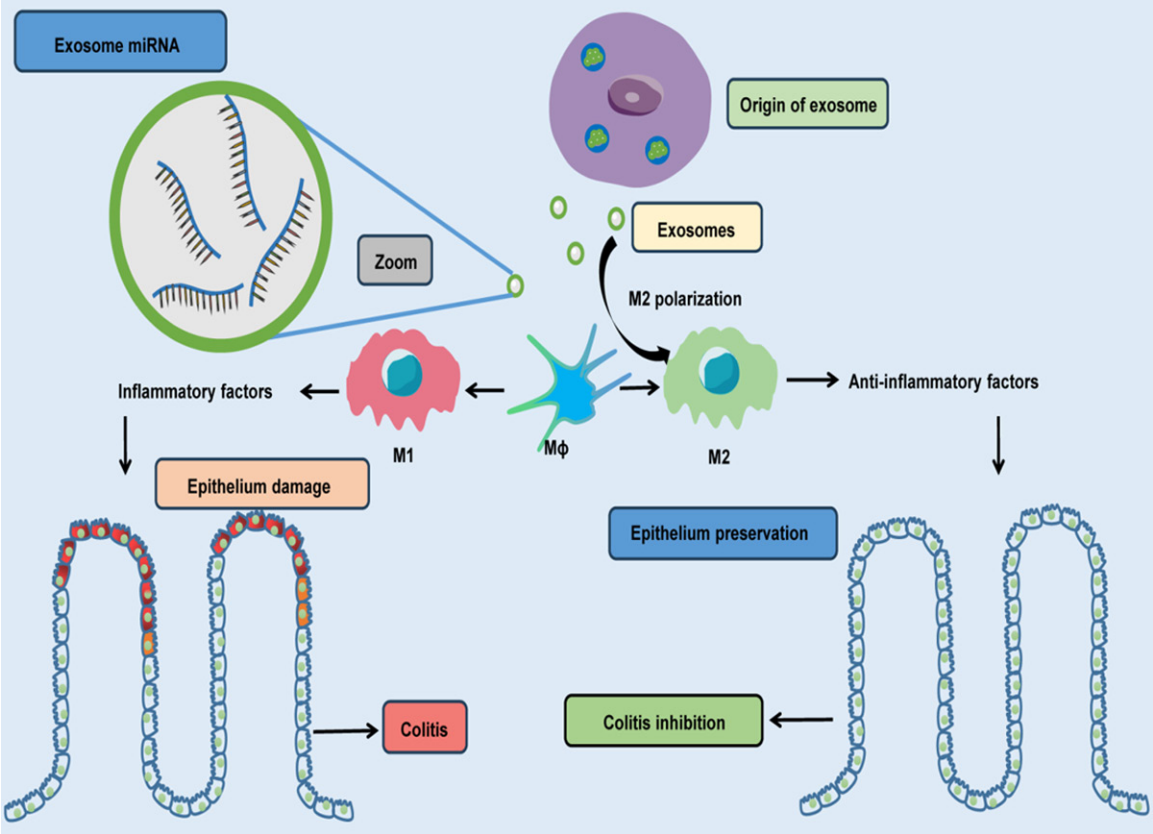

Figure 3. Exosome, exosomal miRNA, and macrophage pathways in IBD repair. Exosomes, including their miRNA, polarize macrophages to M2/activate M2 macrophages. This leads to the production of anti-inflammatory cytokines to repair IBD. Abbreviations: MΦ, inactive macrophage; miRNA, microRNA.

Furthermore, Qingchang Wenzhong decoction (QCWZD) has been found by Lu and team to reduce colonic shortening and mucosal damage by suppressing M1 macrophage polarization and the production of accompanying cytokines, such as IL-6 and TNF-α, in vivo and in vitro [123]. Similarly, it has been discovered that M1 macrophage-induced Caco-2 cell death was reduced by *toxo*ROP16$_{I/III}$-induced M2 macrophages [124]. Importantly, the sEVs of tyrosine-protein phosphatase non-receptor type 1 (Ptpn1)-knockdown macrophages have been reported to be significantly enriched in lactadherin, and recombinant lactadherin therapy reduces intestinal inflammatory response and barrier failure by promoting macrophage M2 polarization [125]. In another study, Song and the team found that both high and low electroacupuncture increased M2 macrophage percentages and lowered M1 macrophages in DSS mice [126]. Liu and the team discovered that berberine regulates the M1 polarization of macrophages in DSS-induced colitis through the AKT serine/threonine kinase 1 (AKT1)/suppressors of cytokine signaling (SOCS) 1/NF-κB signaling pathway [127]. It dramatically lowers the proportion of M1 macrophages [127]. It has also been discovered that phosphatidylmannoside (PtdMan) reduces the levels of proinflammatory cytokines in the colons of RAW264.7 cells and DSS-colitis mice, and it also regulates M1/M2 polarization via activating peroxisome proliferator-activated receptor delta (PPARγ) [128].

The dual role of exosomes in macrophage modulation in IBD

Exosomes produced by healthy cells have favorable benefits; nevertheless, exosomes produced by pathogenic cells, such as cancer cells or infected cells, may have adverse impacts on health [129]. Thus, exosomes play a double role in the regulation of macrophages in IBD. Generally, exosomes derived from healthy stem and stromal cells, food, immune

Table 1. Sources of exosomes or exosome-like nanovesicles modulating macrophages toward IBD repair

Exosomes/exosome-like nanovesicles source	Condition	Mechanism	Reference
Stem/stromal cell			
Hypoxia-prime adipose-derived stem cells	DSS-induced colitis	Control the HMGB1/TLR4/NF-κB signaling pathway to cause macrophage M2 polarization.	[97]
Human umbilical cord MSCs	DSS-induced colitis	Prevent macrophage pyroptosis brought on by casp4 in an inflammatory setting.	[31]
Human bone marrow-derived MSCs	DSS/TNBS induced colitis	Reduce inflammatory reactions, protects intestinal barrier integrity, polarizes M2b macrophages, and stimulates the production of IL-10. Primarily affects colonic macrophages.	[101]
Human umbilical cord MSCs	DSS-induced colitis	Enhance the expression of the IL-10 gene and decreases the infiltration of macrophages, TNF-α, IL-1β, IL-6, iNOS, and IL-7 genes.	[96]
Human umbilical cord MSCs	DSS-induced colitis	Suppress the release of IL-1β from mouse peritoneal macrophages and considerably lowers the relative expression of NLRP3, ASC, caspase-1, IL-18, and IL-1β in macrophages.	[29]
LbL-MSCs	UC	Increase M2 macrophages to control inflammation while decreasing M1 macrophages.	[98]
Human menstrual blood	DSS-induced colitis	Reduce colonic inflammation and polarize M2 macrophages in the colon.	[99]
Bone marrow MSC	DSS-induced UC	Encourage the polarization of M2-like macrophages, which is indicated by a rise in the M2 marker CD163. Upregulate TGF-β and IL-10 and downregulate TNF-α, CCL-24, TNF-α, VEGF-A, and IFN-γ levels.	[100]
Macrophage			
M2	DSS-induced colitis	MiR-590-3p, highly concentrated in M2 exosomes, suppresses the production of proinflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor-α.	[49]
M2	DSS-induced colitis	Inhibit IL-1β, IL-6, and IL-17A. Offer protection against colitis produced by DSS, mostly through the CC chemokine 1 (CCL1)/CCR8 axis.	[11]
Food			
Turmeric	Colitis	It increase the M1 phenotype's transition to M2 macrophages and restores the impaired gut epithelial barrier.	[112]
Ginseng	DSS-induced colitis	Stimulate the synthesis of anti-inflammatory macrophages while downregulating proinflammatory cytokines in proinflammatory macrophages.	[113]
Spermidine	DSS-induced colitis	Increase the markers for M2 macrophages while decreasing the markers for M1 macrophages in the inflammatory colons.	[115]
Colostrum	DSS-induced UC	Stimulate the growth of macrophages and colonic epithelial cells, reduce inflammation by efficiently eliminating ROS, and control the release of immune cytokines.	[50]
Milk	DSS-induced UC	Reduce the inflammatory response by blocking the activation of the NLRP3 inflammasome and the TLR4-NF-κB signaling pathway. Stop the release of cytokines and macrophage polarization toward a proinflammatory phenotype.	[116]
Other exosomes/EVs			
Trichinella spiralis	DSS-induced colitis	Activate M2 macrophages in the colon and prevent M1 macrophage polarization.	[117]
HEK293T cells	Sepsis-induced intestinal damage	Minimize systemic inflammation and mortality while promoting M2 polarization by reducing mitochondrial reactive oxygen species (mtROS).	[118]
Other immune cells			
G-MDSC	DSS-induced colitis	The G-MDSC exosome (containing Arg-1) inhibits the delayed-type hypersensitivity response, reduces the growth of CD4+ T cells, and decreases IFN-γ and TNF-α levels.	[110]

Abbreviations: ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; DSS, dextran sulfate sodium; G, granulocytic; HMGB1, high mobility group box 1; IFN-γ, interferon-gamma; IL, interleukin; ILVs, intraluminal vesicles; iNOS, inducible nitric oxide synthase; M, macrophage; MDSC, myeloid-derived suppressor cells; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family, pyrin domain-containing 3; ROS, reactive oxygen species; TGF-β, transforming growth factor beta; TLR4, Toll-like receptor 4; TNBS, 2,4,6-trinitrobenzenesulfonic acid solution; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

cells, and other systems or pathogens regulate macrophages toward IBD repair (**Table 1**); however, those derived from inflammatory-driven cells and unhealthy cells aggravate IBD and its progression.

Exosomes and their microRNA, driven by inflammatory stimuli, immune cells, and disease cells, regulate macrophages to support IBD and its progression. For instance, exosomal miR-93-5p secreted by granulocytic myeloid-

derived suppressor cells (G-MDSC) in response to IL-6 encourages the development of monocytic MDSCs (M-MDSC) into M2 macrophages and involves a signal transducer and activator of transcription 3 (STAT3) signaling route that promotes the progression from colitis to malignancy [130]. Besides, treatment of RAW264.7 macrophages with serum exosomes derived from mice induced by DSS encourages phosphorylation of p38 and extracellular signal-regulated kinase (ERK) as well as the generation of TNFα [131]. Additionally, Gong and colleagues have demonstrated that serum exosomes (from CD) may circulate into the intestine's mucosa and greatly exacerbate colitis by controlling macrophage activation and the function of the epithelial barrier [132]. Moreover, CD14+ Mφ contributes to CD pathogenesis by causing activation-induced cell death (AICD) opposition in CD4+ T cells by releasing TNF in the exosomal membrane and activating TNFR2/NF-κB signaling [133].

Conclusion and perspective

IBD, which includes both UC and CD, is a complex illness with an unknown cause. Immune cells involved in IBD, such as macrophages, emit cytokines and chemokines that promote inflammation and compromise intestinal barrier integrity. It has been discovered that M1 macrophages exacerbate IBD, while M2 macrophages mitigate the disease. Exosomes, as ubiquitous conveyors of intercellular messages, are involved in immune mechanisms and immune-mediated disease processes. Additionally, exosomes derived from healthy stem and stromal cells, food, immune cells, parasites, and other artificial systems have been shown to regulate macrophages toward IBD repair. Moreover, other compounds have also been found to regulate macrophages toward IBD repair. However, exosomes from inflammatory-driven and disease cells promote M1 macrophages to perpetuate IBD. Therefore, in the future, more studies should be done on immune cell-derived exosomes and their modulation of macrophages to repair IBD. Also, immune cell-derived exosomes other than macrophages should be explored to determine the mechanism that regulates macrophages toward IBD repair.

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Disclosure of conflict of interest

None.

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