Supplementary material Table 2. Mechanisms of exosomes/exosomal components which have potential effects on IBD.

Components	Function	Origins	Effects/Mechanisms	Significance	Functions of exosome structure	Reference
Exosomal lncRNAs						
LncRNA GAS5	Long, non-coding RNA up regulates glucocorticoid in-resistant cells	—	Promotes apoptosis of macrophages or inhibits glucocorticords activity	Treatment	Membrane carrier of high level lncRNA GAS5	[1; 2]
Exosomal miRNAs						
MiR155	Short RNA molecules binding to specific mRNAs to regulate protein production or cause RNA cleavage; Stimulates endothelium barrier dysfunction and intestinal inflammation in IBD	Macrophages, DCs, KLF5-overex pressing VSMCs	Deficiency of exosomal miR155 may ameliorate intestinal inflammation by suppressing the development and function of CD103+CD11b+DC in the lamina propria of intestine in IBD; KLF5-overexpressing VSMCs-derived exosomes loaded with miRNA155 can transport into ECs to modulate endothelium barrier dysfunction through downregulation of TJ protein expression and disruption of this process may alleviate IBD	Treatment	As a paracrine messenger to mediate the cell-cell communication	[3; 4; 5]
MiR146b	Up regulates NF-κB to accelerate IBD inflammation	DCs	Aggravates intestinal inflammation by up regulating NF-κB and deficiency of it may ameliorate IBD course	Treatment	Membrane carrier	[6; 7]
MiR1246	Activates macrophages and T cells to aggravate IBD inflammation	Detected in sera	Suppresses the anti-inflammation by reprogramming macrophages or activates the proinflammatory nuclear factor of activated T cells, and may contribute to the effective indication as a biomarker of active IBD	Treatment/ Diagnosis	Drives macrophage reprogramming	[8; 9]
MiR16	Activates NF-κB signaling pathway to accelerate UC	Detected in human milk	Inhibition of adenosine A2a receptor expression to activate NF-κB signaling pathway in UC	Treatment	Able to survive digestion and being taken up by enterocytes	[10; 11]
MiR29b	Up regulates in active UC	Detected in bovine milk	Accumulated and transported by colon cells in IBD; Up regulates in active UC	Treatment	Able to survive digestion and being accumulated and	[12; 13]

					transported by intestinal mucosal cells to peripheral tissues	
MiR200c	Up regulates in IBD	Detected in bovine milk	Up regulates and affects gasotransmitter pathways in IBD	Treatment	Able to survive digestion and being transported by intestinal mucosal cells to across the basolateral membrane for subsequent delivery to peripheral tissues	[12; 14]
MiR223	Activates NLRP3 inflammasome and facilitates the release of IL-1β and IL-18 to alleviate colitis	Thrombin-activated platelets	Down regulates MAPK and NF-κB pathway to inhibit ICAM-1 expression in inflammation; Exosomal miR223 may regulate the activation of the NLRP3 inflammasome and the release of IL-1β and IL-18 to attenuate early colitis	Treatment	Membrane carrier	[15; 16]
MiR22	Up regulates in CD	Detected in human milk	Stimulates CD progress	Diagnosis	Able to survive digestion and being taken up by enterocytes	[13; 17]
MiR375	Up regulates in active CD	Detected in serum	Stimulates active CD progress	Diagnosis	Provides stability for cell-free miR375 in various bodily fluids	[13; 18]
MiR150	Down regulates c-Myb and Bcl-2 to induce colonic EC apoptosis in active IBD	IEC-6	Down regulates c-Myb and Bcl-2 expression to induce colonic EC apoptosis in active IBD and deficiency of it may contribute to IBD therapy	Treatment	—	[19; 20]
Exosomal proteins						
ANXA2	A protein facilitates phagocytosis of apoptotic ECs	—	Exosomal Annexin A2 activation enhances phagocytosis of apoptotic ECs, while its inhibition may prevent membrane-anchored TNF-α shedding in IBD	Treatment	Membrane carrier	[21; 22]
Ubiquitinated HLA-G	Secreted soluble molecules belonging to the non-classical HLA class I family; Expresses only on	HLA-G1-transfected cells	Modulates immune-regulatory tolerance, the secretion of IL-10 in response to inflammation and the mucosal immunity in UC	Treatment	Membrane carrier	[23; 24]

	maternal–fetal interface and immune privileged adult tissues					
S100A8	A pro-inflammatory protein increased in serum and mucosa of IBD children	MDSC	Potential new biomarker in IBD diagnosis or regulates T cell responses	Treatment/ Diagnosis	Membrane carrier	[25; 26]
S100A9	A pro-inflammatory protein increased in serum and mucosa of IBD children	MDSC	Facilitates UC by activating STAT3 or T cell responses and down regulation of it may contribute to IBD therapy	Treatment	Membrane carrier	[25; 26]
TG2	A functional enzyme increased in IBD	TG2 proficient cells	Inhibition of exosomal TG2 may contribute to IBD treatment	Treatment	Membrane carrier	[27; 28]
Complement C3	An inflammatory protein	Intestinal lymph	Potential autoantigen in IBD	Diagnosis	Membrane carrier	[29; 30; 31]
Complement C5	Aggravates colitis by up regulating the mucosal expression of TNF-α, IL-1β and IL-6	Intestinal lymph	Inhibition of exosomal complement component C5 may ameliorate colitis by reducing the mucosal expression of TNF-α, IL-1β and IL-6	Treatment	Membrane carrier	[29; 30; 31]
Fibronectin	Induces colitis	Intestinal lymph	Induces colitis mediated by integrin-linked kinase	Diagnosis	Membrane carrier	[32; 33]
Plasminogen	Increased in UC	Intestinal lymph	Indicates clinical activity of UC	Diagnosis	Membrane carrier	[34; 35]
Thymic stromal lymphopoietin	Products of harmless antigens	IEC	Involves in the conditioning of DCs in IBD	Treatment	Membrane carrier	[36]
Integrin αvβ6	Involving in the tolerogenic DC conditioning.	IEC	Increased expression of TGF-β in DC conditioning and Treg cell induction in IBD	Treatment	Membrane carrier	[36]
Beta-defensin 2	Anti-microbial peptides	IEC apical side	Exosomes from IEC apical side may be stimulated by protozoan parasite Cryptosporidium parvum to produce and secret in the luminal through the activation of TLR4 signaling	Treatment	Membrane carrier	[36]
Cathelicidin-37	Anti-microbial peptides	IEC apical side	Exosomes from IEC apical side may be stimulated by protozoan parasite Cryptosporidium parvum to produce and secret in the luminal through the activation of TLR4 signaling	Treatment	Membrane carrier	[36]
GRP78	As an endoplasmic reticulum stress marker	Unclear	Maintains normal colonic epithelium function in IBD	Treatment	As a paracrine messenger to mediate	[37; 38]

	protein to maintain normal colonic epithelium function in IBD				the cell-cell communication, or as a biomarker of disease	
PrPC	A glycosylphosphatidylinositol-anchored glycoprotein located in cell–cell junctions and interacts with desmosome proteins in the intestinal epithelium	Platelet	Regulates TJ barrier function in both UC and CD	Treatment	Membrane carrier	[39; 40]
Peroxisome proliferator-activated receptor-γ	A nuclear receptor regulates differentiation and proliferation of adipocyte, and functions of immune cells as well as inflammatory cells	Human plasma	Contributes to the paracrine transfer of nuclear receptors in IBD, especially UC and down regulation of it may contribute to IBD therapy	Treatment	Membrane carrier	[41; 42]
Albumin	Mediated by TNF to induce IBD	Intestinal lymph	Mediated by TNF to induce IBD and downregulation of it may contribute to IBD therapy	Treatment	Membrane carrier	[29; 30; 31]
HSP70 protein family (including HSP72 and HSP73)	Regulates lymphocyte activity and cytokine production	—	Exosomal HSP70 protein may regulate lymphocyte activity and cytokine production; HSP72 may regulate intestinal microbiota profile	Diagnosis/ Treatment	—	[43; 44]
Special contents						
Sphingosine-1-phosphate, CCL20, prostaglandin	CCL20 (cytokine) and prostaglandin (pro-inflammatory mediator) involve in the recruitment and proliferation of Th17 cells; Sphingosine-1-phosphate((human sequence-specific DNA binding protein) stimulates the production of CCL20+PGE2+S1P+	Intestinal mucosa	Stimulated by ET-BSPs exosomes, may modulate E2-required proliferation of Th17 cells through the MyD88-mediated pathway and cause intestinal inflammation in IBD	Treatment	As a membrane carrier to involve in intracellular communication across species	[45]

	exosomes					
Cholesterol	A kind of lipid suppresses IBD inflammation or even inhibits pyroptosis signaling to alleviate IBD	—	Inhibits pyroptosis signaling to ameliorate experimental colitis	Treatment	Membrane carrier	[46; 47]
Glucosylceramide	A kind of lipid suppresses IBD inflammation	—	Suppresses colon inflammation in IBD or bind with CD1 to inhibit activation of NK T cells in intestinal epithelium	Treatment	Membrane carrier	[48; 49]
Lysophosphatic acid	A kind of lipid activates proinflammatory mediators of IBD	—	Activates proinflammatory mediators in the arachidonic pathway in chronic colitis and down regulation of it may contribute to IBD therapy	Treatment	Membrane carrier	[46; 50]
Phosphatidylcholine	A kind of lipid induces inflammation in UC	—	Inhibitory effects of corticosteroid in patients with chronic steroid-refractory UC, or induce inflammation in UC and down regulation of it may contribute to IBD therapy	Treatment	Membrane carrier	[46; 51]
Sphingomyelin	A kind of lipid alleviates inflammation	Mainly from B-lymphocyte	Modulates inflammation by activating peroxisome proliferator-activated receptor-γ, and decreased exosomal sphingomyelin of it may activate cathepsin D as a mediator of apoptosis related to disruption of epithelial barrier in IBD	Treatment	Membrane carrier	[46; 52]
Phosphatidylinositol	A kind of lipid	Mainly from B-lymphocytes, mast cells and DCs	Deficiency of exosomal phosphatidylinositol may protect against endoplasmic reticulum stress in IBD	Treatment	Membrane carrier	[46; 53]
Curcumin	A polyphenol derived from the herbal remedy and dietary spice turmeric	Detected in milk	Alleviation of IBD	Treatment	Provides stability in PBS; Survives digestion and being easier to cross the intestinal barrier	[54]

Note: ANXA2, Annexin A2; ApoA-I, apolipoprotein A-I; CCL20, C-C motif chemokine 20; CD, crohn's disease; circRNAs, circular RNAs; CLDN8, claudin-8; DC, dendritic cell; DSS, dextran sulfate sodium; EC, epithelial cell; EGFR, epidermal growth factor receptor; ET-BSP, enterobacteria; GAS5, growth arrest-specific 5; HLA-G,

human leukocyte antigen-G; HSP, heat shock protein; IBD, inflammatory bowel disease; ICAM, intercellular adhesion molecule; IEC, intestinal epithelial cell; IFN-γ, gamma interferon; IL, interleukin; KLF, Krüppel-like factor; lncRNA, long none coed RNA; MAPK, mitogen-activated protein kinase; MDSC, myeloid-derived suppressor cell; miRNA, microRNA; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor-kappaB; NK, natural killer; PrPC, cellular prion protein; TJ, tight junction; Tregs, regulatory T cell; TG2, transglutaminase type 2; TNF, tumor necrosis factor; UC, ulcerative colitis; VSMCs, vascular smooth muscle cells

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