Figure S1. Mechanisms of intestinal endotoxemia and multiorgan dysfunction caused by sepsis. Sepsis induces gut barrier injury and LPS translocation, leading to endotoxemia. LPS activates TLR4/TRIF and STING/TBK1 pathways and ERK signaling in macrophages, upregulates miR-155 and suppresses AMPK, thereby activating NLRP3 inflammasome. These events drive M1 polarization and excessive inflammation, resulting in endotoxemia and multiple organ dysfunction. LPS, lipopolysaccharides; TLR4, Toll-like receptor 4; IRF3, interferon regulatory factor 3; TBK1, TANK binding kinase 1; STING, stimulator of interferon genes; DNA, deoxyribonucleic acid; miR, microRNA; AMP-activated protein kinase; ERK, extracellular signal-regulated kinase; NLRP3, NOD-like receptor protein 3; PAMPs, pathogen-associated molecular patterns; MyD88, myeloid differentiation factor 88; TNF-α, tumor necrosis factor; AMPK, AMP-activated protein kinase; IFNs, interferons; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; IL, interleukin; Arg1, arginase 1; TGF-β, transforming growth factor-β; TRIF, TIR domain-containing adaptor molecule 1; DAMPs, damage-associated molecular patterns.

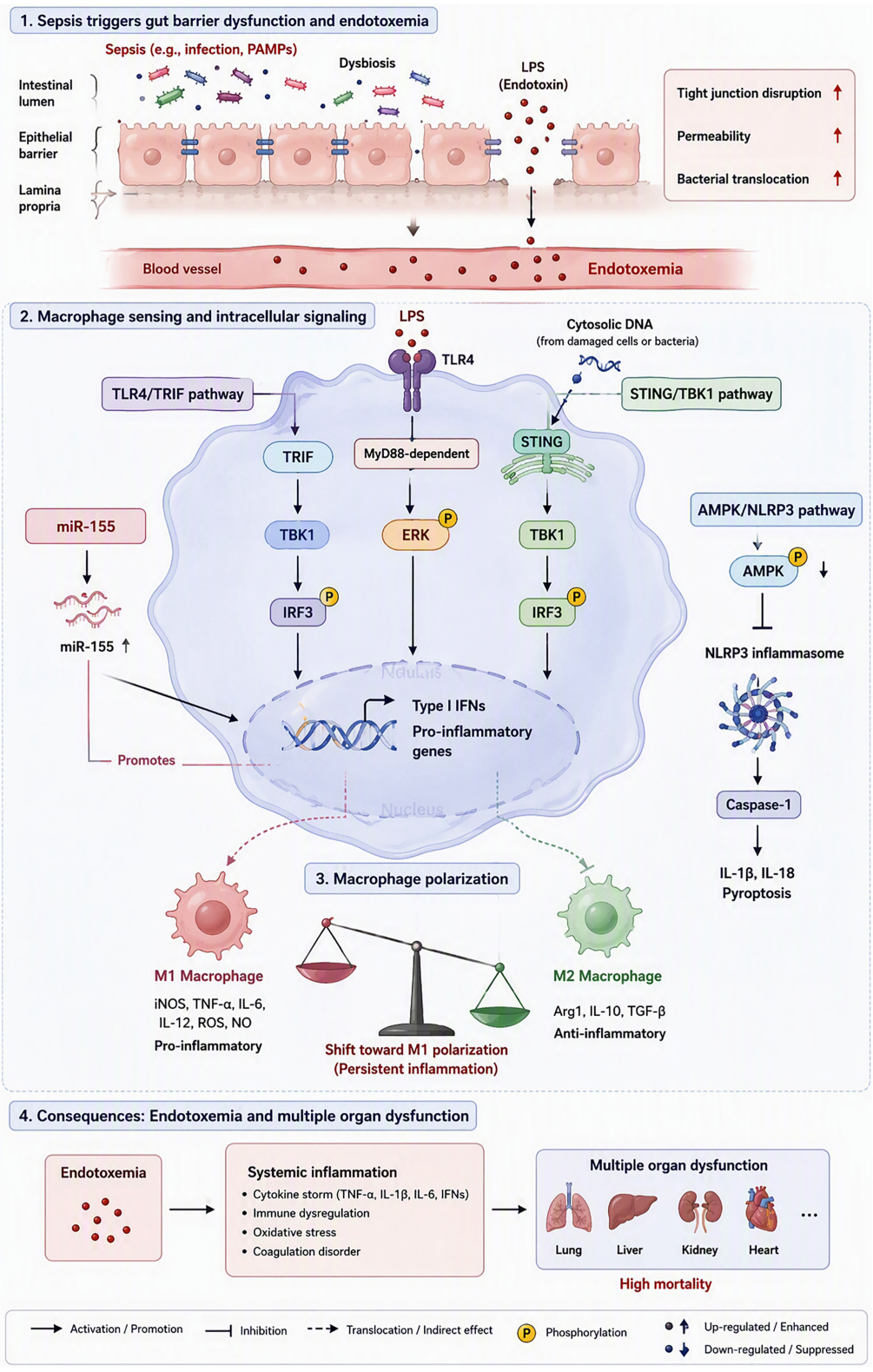


Figure S2. Mechanism of infection leading to multiple organ failure during sepsis. The infection site triggers a local inflammatory response, activating the immune system through recognition of PAMPs and DAMPs. This leads to immune cell activation and exacerbation of systemic inflammation. Inflammatory mediators, such as TNF-α and IL-1 and IL-6) cause vascular endothelial dysfunction, coagulopathy, tissue damage, intestinal barrier disruption and multiorgan failure. PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; TNF-α, tumor necrosis factor; IL, interleukin; PPR, pathogen recognition receptor.

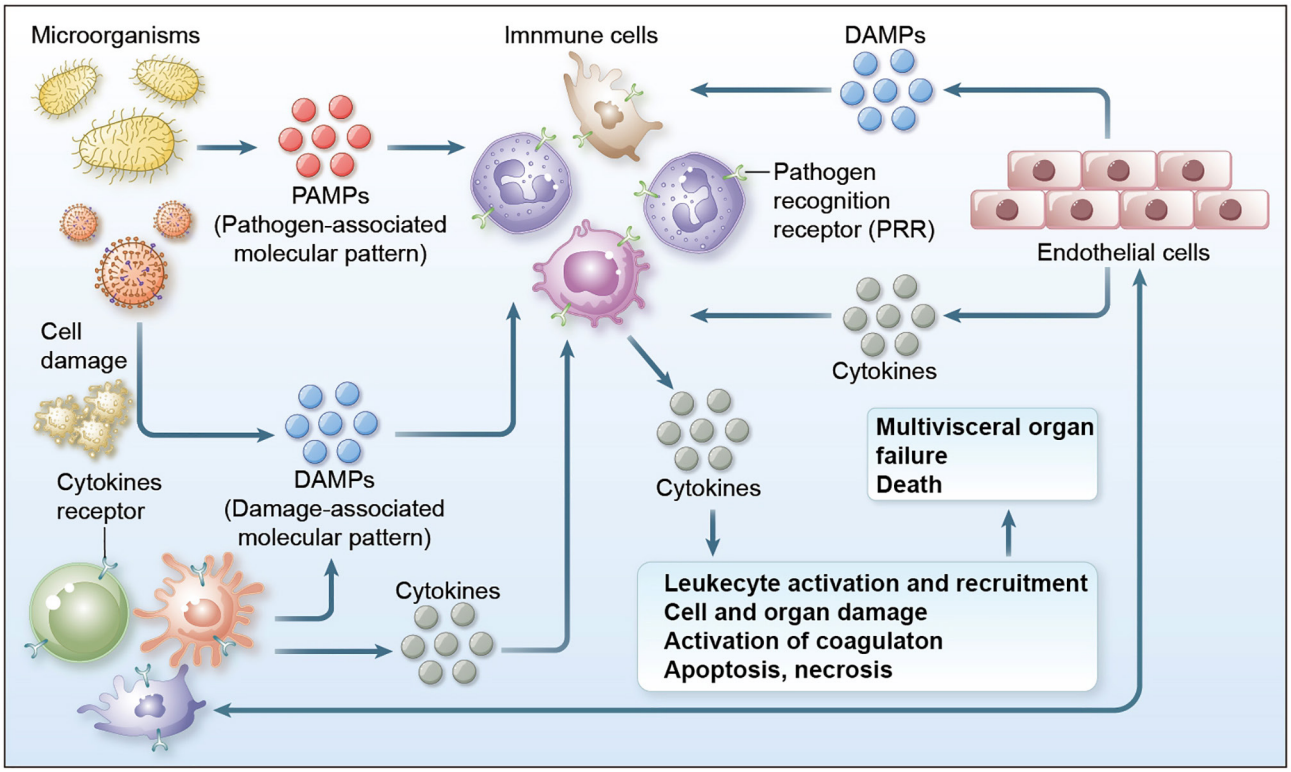


Figure S3. Composition of the intestinal mucosal barrier. Epithelial cells form a monolayer that acts as a physical barrier, with tight junctions between cells reinforcing this function. Several tight junction proteins seal the paracellular pathway, performing both gate and fence functions. The mucosal layer serves as a chemical barrier that is crucial for restricting direct contact between the microbiome and epithelial cells. Immune cells within the mucosa are key contributors to immune responses and host tolerance to external substances. LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; ILCs, innate lymphoid cells; AMPs, antimicrobial peptides; SFB, segmented filamentous bacteria; SCFA, short-chain fatty acid; PSA, prostate-specific antigen; TCR, T-cell receptor; IEL, intestinal intraepithelial lymphocytes.

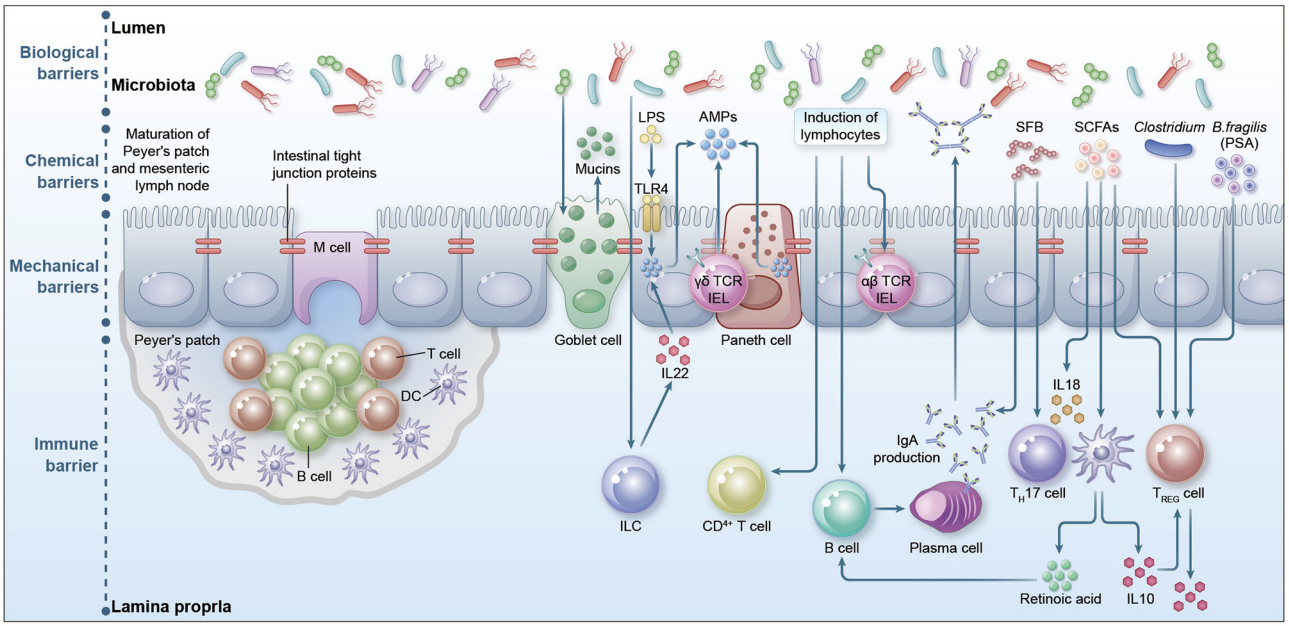


Figure S4. Mechanism of sepsis-induced intestinal mucosal injury. During sepsis, systemic inflammation disrupts intestinal microvascular perfusion, leading to intestinal ischemia, mucosal injury and cellular dysfunction. This inflammation can directly damage intestinal epithelial cells, causing apoptosis and increasing intestinal mucosal permeability. The integrity of the intestinal barrier relies on the normal expression and function of tight junction proteins, which are compromised by the activation of inflammatory mediators during sepsis. Increased intestinal permeability allows endotoxins and inflammatory cytokines to enter the bloodstream, contributing to multiorgan dysfunction. PAMPs, pathogen-associated molecular patterns.

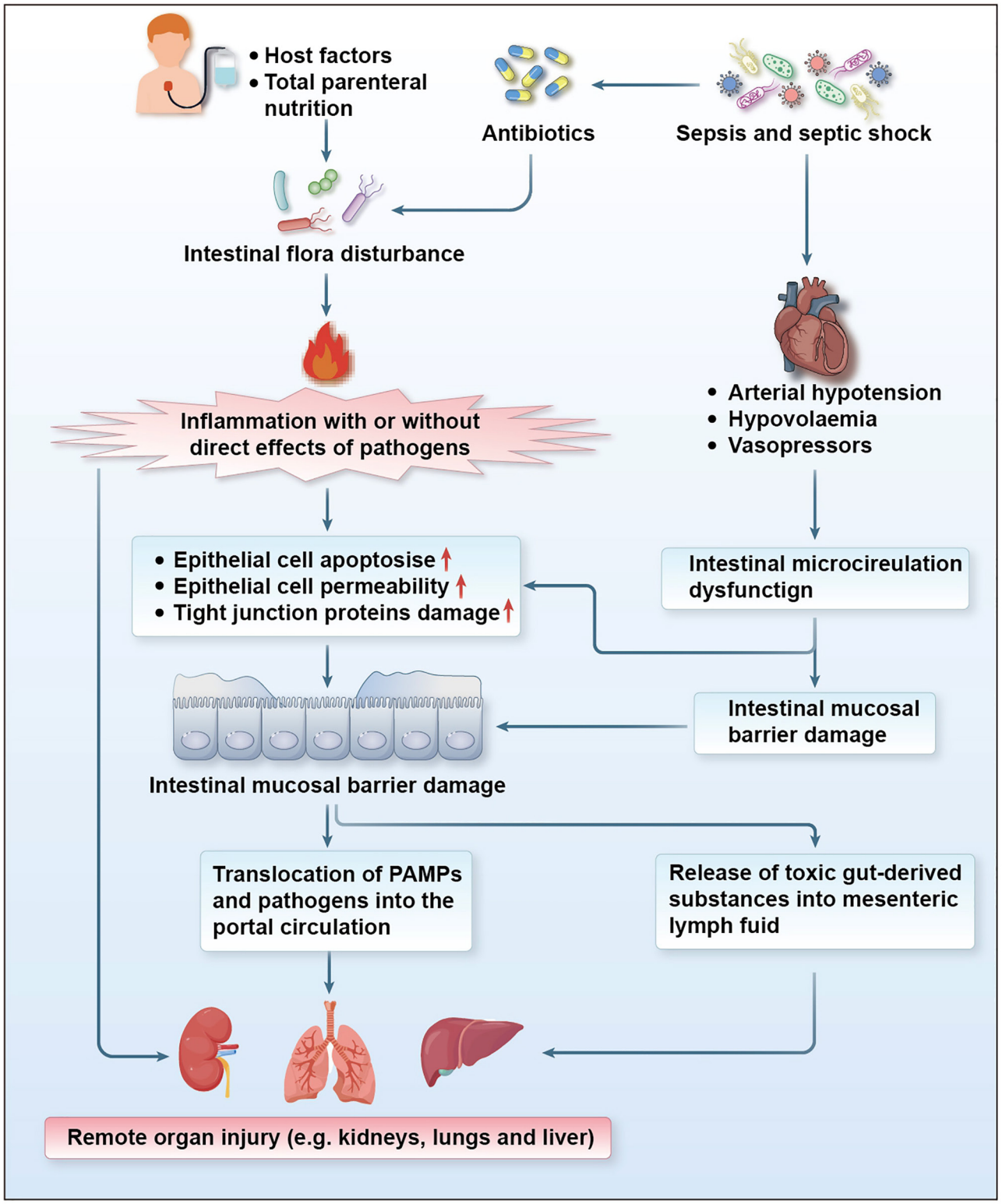


Figure S5. Mechanism of intestinal microcirculation damage caused by sepsis. During sepsis, LPS increase MMP-9 activity through the TLR4/MyD88/NF-κB pathway, resulting in degradation of the intestinal mucosal vascular basement membrane and increased vascular permeability. LPS also triggers the release of NETs, which obstruct intestinal mucosal microvessels. Inflammatory cytokines inhibit SphK1 activity, leading to detachment of the endothelial glycocalyx and further increasing intestinal vascular permeability. Following endothelial injury, TF is released, activating extrinsic coagulation pathways and promoting the formation of intestinal mucosal capillary microthrombi. Platelet activation leads to adhesion and occlusion of microvessels by platelets and WBCs. Additionally, increased catecholamine release causes intestinal microvascular constriction. Collectively, these processes contribute to intestinal ischemia, hypoxia, mucosal edema and congestion. LPS, lipopolysaccharide; MMP-9, matrix metallopeptidase 9; Syn, synaptophysin; decan-1, Decan-1-amine; α7nAchR, α7 nicotinic acetylcholine receptor; TLR4, Toll-like receptor 4; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor-kappa B; SphK1, sphingosine kinase 1; NETs, neutrophil extracellular traps; SphK1, sphingosine kinase 1; TF, tissue factor; WBCs, white blood cells.

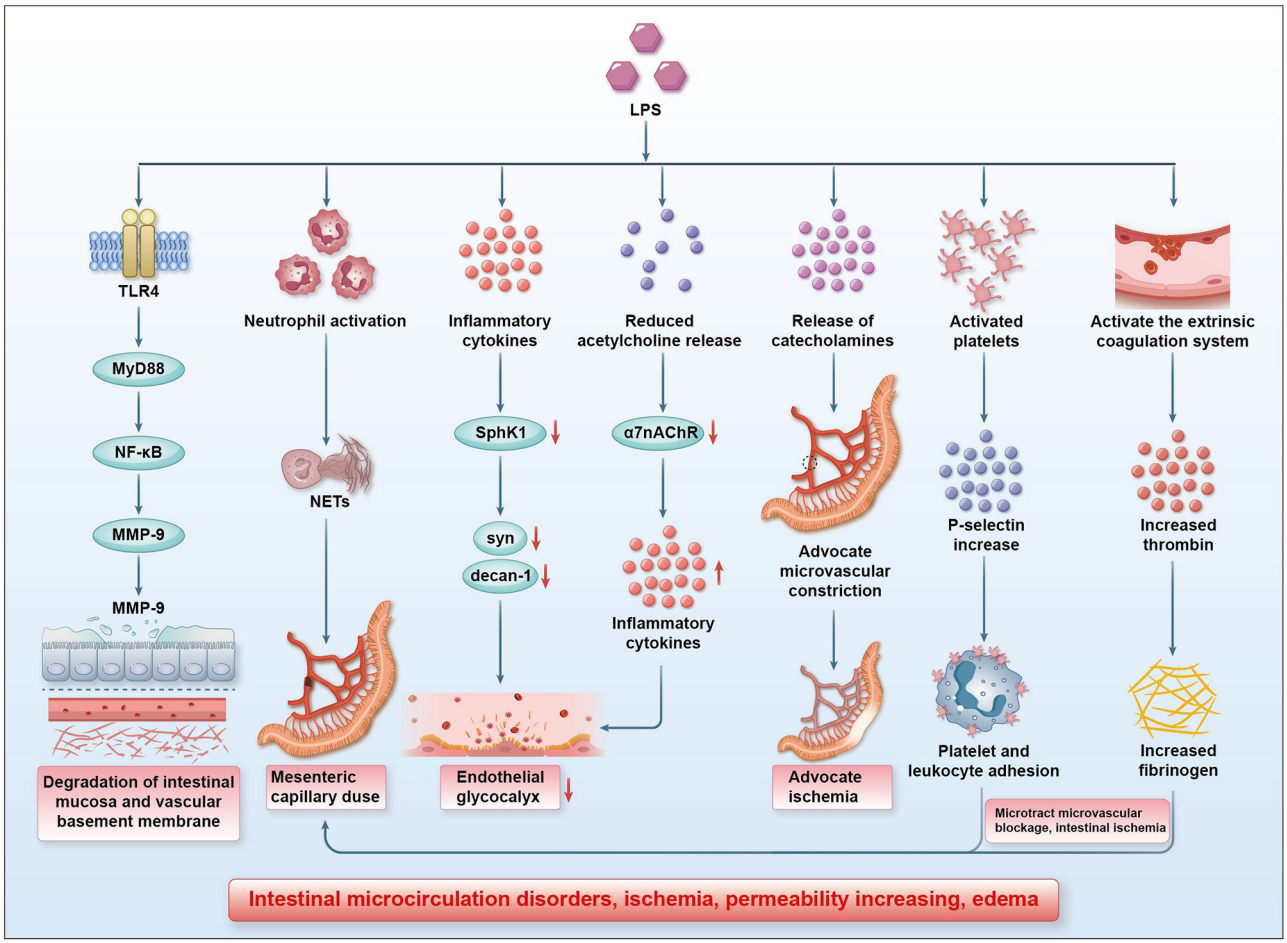


Figure S6. Mechanism of sepsis-induced damage to intestinal mucosal epithelial cells. During sepsis, LPS activates the TLR4, JAK2/STAT3 and MAPK pathways, stimulating NF-κB and promoting the release of inflammatory factors, leading to intestinal epithelial cell damage. Activation of the NLRP3/caspase-1 pathway increases the expression of pyroptosis-related proteins IL-8 and ASC, promoting pyroptosis in intestinal epithelial cells. Inhibition of the Nrf2/HO-1 pathway reduces the levels of antioxidant enzymes such as SOD and GSH, increasing ROS levels and causing oxidative stress in intestinal epithelial cells. Activation of the PI3K/AKT/TSC2 pathway inhibits mTOR activity and promotes autophagy. Inhibition of the SIRT1 and SIRT3/FoxO3a pathways reduces Nrf2 expression and increases GPX4 and SLC7A11 expression, leading to ferroptosis in intestinal epithelial cells. Regulation of MLCK promotes MLC phosphorylation, causing actin contraction around tight junctions, detachment of ZO-1 from the cell membrane and increased intestinal permeability. LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; JAK2, Janus kinase 2; STAT, signal transducer of activation; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor κB; NLRP3, nod-like receptor protein 3; ASC, apoptosis-associated speck-like protein containing a CARD; HO-1, heme oxygenase-1; Nrf2, nuclear factor erythroid 2-related factor 2; SOD, superoxide dismutase; GSH, glutathione; ROS, reactive oxygen species; MLCK, myosin light-chain kinase; ZO-1, zonula occludens-1; MLC, myosin light chain; PI3K, phosphoinositide 3-kinase; TSC2, tuberous sclerosis complex 2; SIRT1, sirtuin 1; mTOR, mammalian target of rapamycin; Akt, protein kinase B; IL, interleukin; TNF-α, tumor necrosis factor-alpha; ASC, apoptosis-associated speck-like protein containing a CARD; GSDMD, gasdermin D; LC3A, microtubule-associated protein 1 light chain 3 alpha; Atg15, autophagy-related protein 15; Sirt3, Sirtuin 3; FOXO3a, Forkhead box O3a; p-MLC, Phosphorylated myosin light chain; ZO-1, Zonula occludens-1; Beclin-1, Bcl-2-interacting coiled-coil protein 1; GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7a member 11.

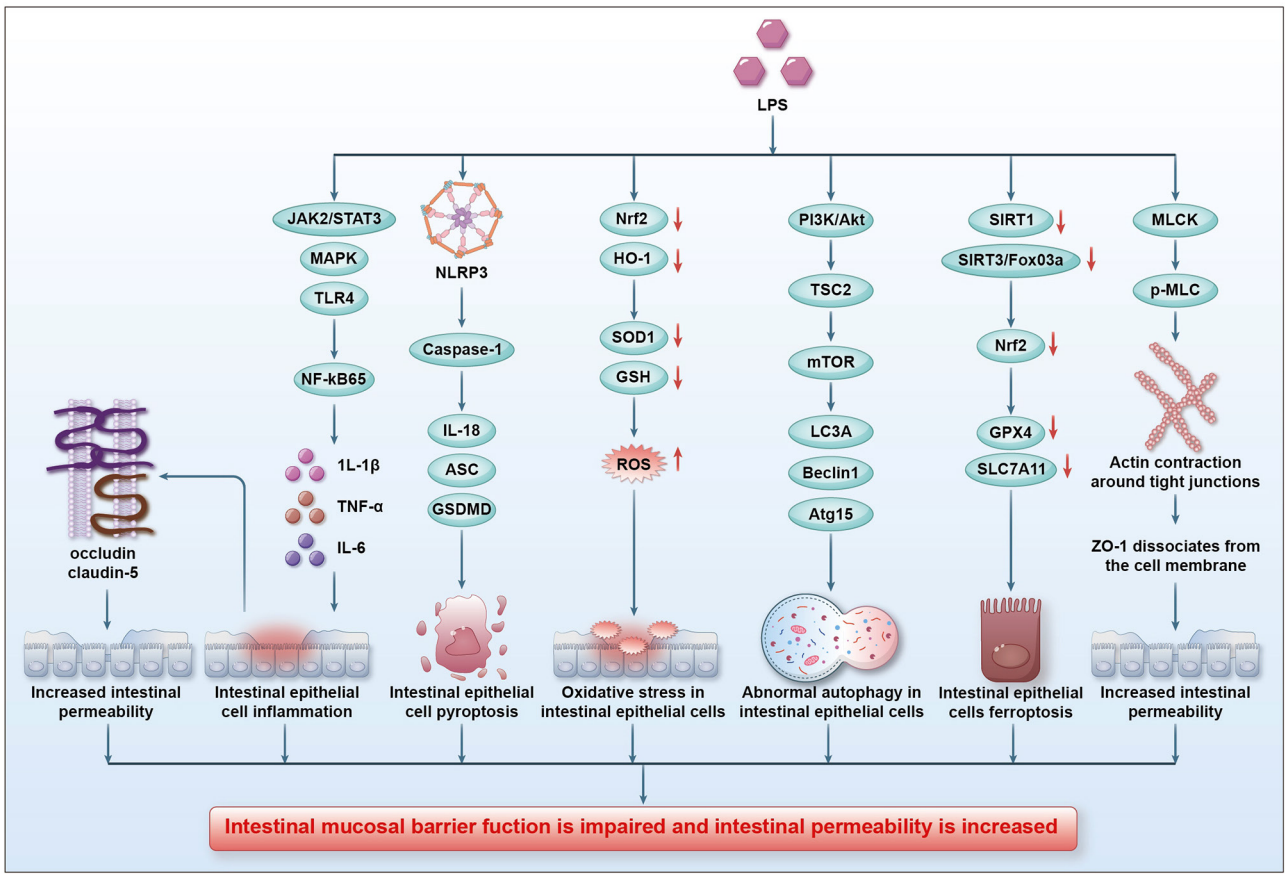


Figure S7. Mechanism of sepsis-induced damage to intestinal tight junction proteins. During sepsis, TNF-α activates NF-κB, inhibiting the transcription of tight junction proteins such as occludin and claudin-5. IL-6 downregulates claudin-1 and ZO-1 expression through the JAK/STAT3 pathway. Following activation of TLR4/MyD88, claudin-1 and occludin are downregulated, whereas claudin-2 is upregulated. ROS activate matrix metalloproteinases (such as MMP-9), leading to degradation of claudin-5 and ZO-1. The antioxidant pathway Nrf2/ARE is impaired, exacerbating oxidative damage to tight junction proteins. Increased Caspase-3/8 and Bax/Bak activity promotes intestinal epithelial cell shedding and tight junction dysfunction. TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor-kappa B; IL, interleukin; ZO-1, zonula occludens-1; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; TLR4, Toll-like receptor 4; MyD88, myeloid differentiation factor 88; MMP-9, matrix metallopeptidase 9; BAX, BCL2-associated X protein; RhoA, Ras homolog family member A; ROCK, Rho-associated coiled-coil containing protein kinase; ROS, reactive oxygen species; BAK, BCL2 antagonist/killer; Nrf2, nuclear factor erythroid 2-related factor 2; ARE, antioxidant responsive element; TJs, tight junction proteins.

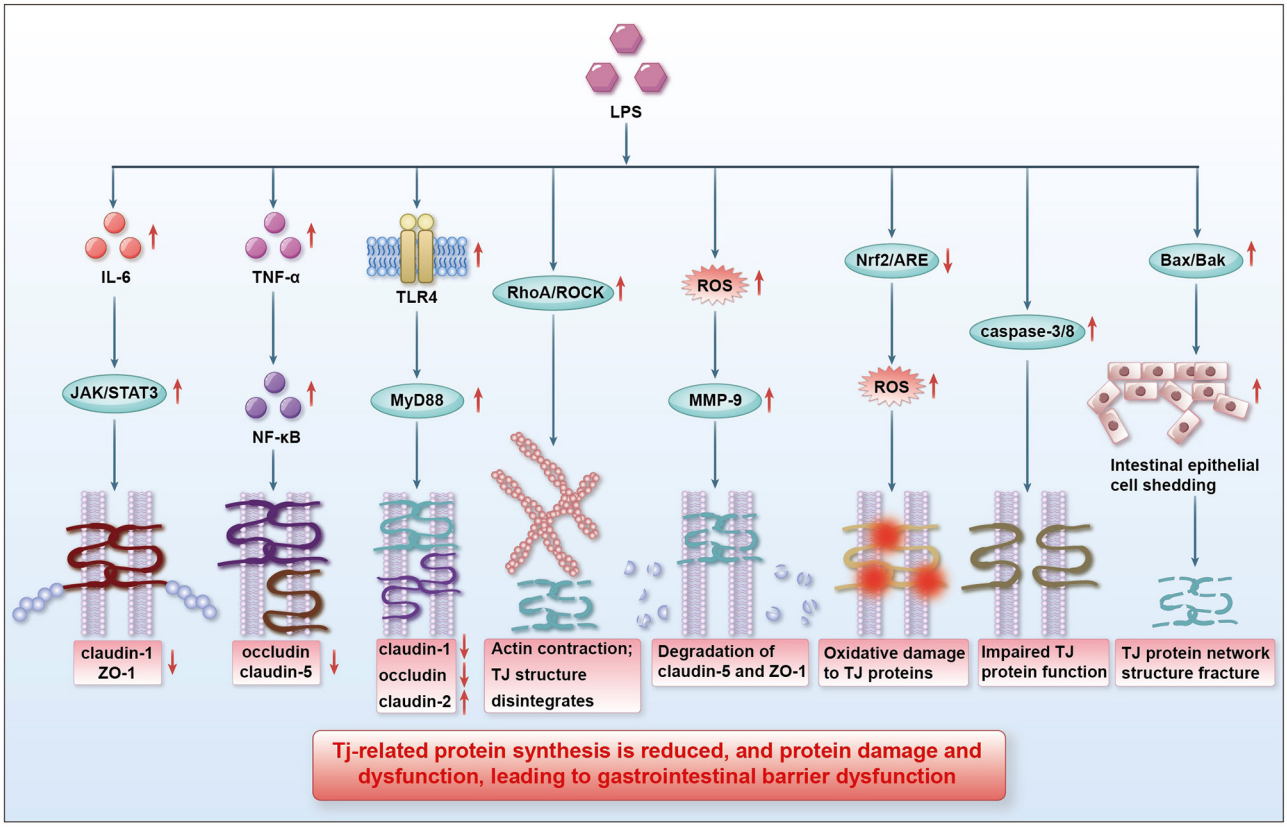


Figure S8. Origin and function of macrophages. Macrophages are versatile immune regulation and tissue homeostasis through phagocytosis, antigen presentation, cytokine production immune modulation and tissue repair.

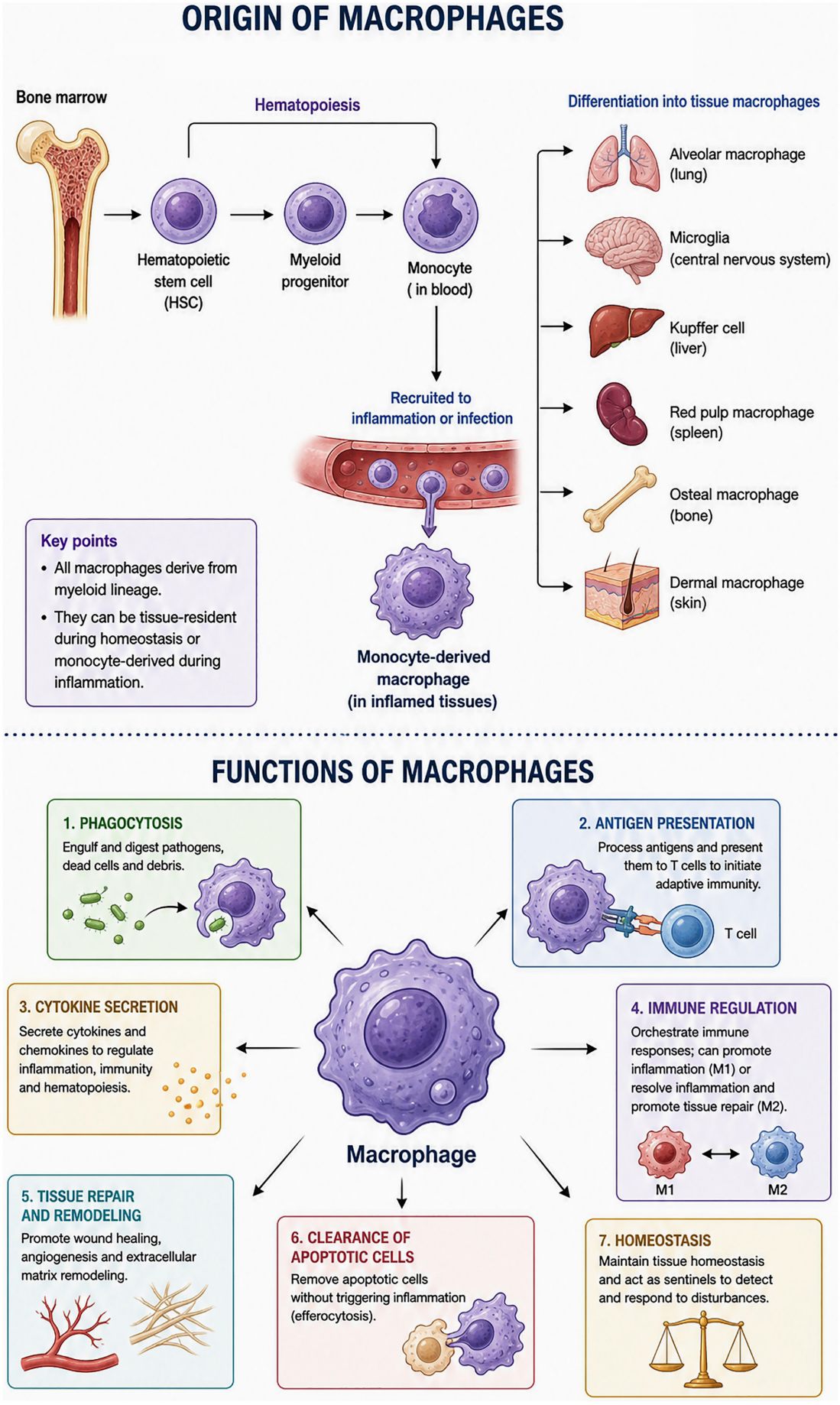


Figure S9. Influence of different stimulating factors on the direction of macrophage differentiation. Macrophages can polarize into M1 (proinflammatory) or M2 (anti-inflammatory) macrophages, depending on the type of stimuli they encounter. Based on the stimuli and resulting transcriptional changes, M2 macrophages can be further categorized into four subtypes: M2a (activated by IL-4 or IL-13), M2b (activated by immune complexes and LPS), M2c (activated by glucocorticoids or IL-10) and M2d (activated by adenosine or IL-6). M1 macrophages are primarily induced by IFN-γ and LPS stimulation. Phenotypically, M1 macrophages produce high levels of proinflammatory cytokines, mediate resistance to pathogens and exhibit strong bactericidal and antitumor activities. TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor; CD, cluster of differentiation; IL, interleukin; VEGF, vascular endothelial growth factor; M1, M1 macrophages; M0, M0 macrophages; M2a, M2a macrophages; M2b, M2b macrophages; M2c, M2c macrophages; M2d, M2d macrophages; TAMs, tumor-associated macrophages; MHCII, major histocompatibility complex class II; Arg-1, arginase 1; MR, mineralocorticoid receptor.

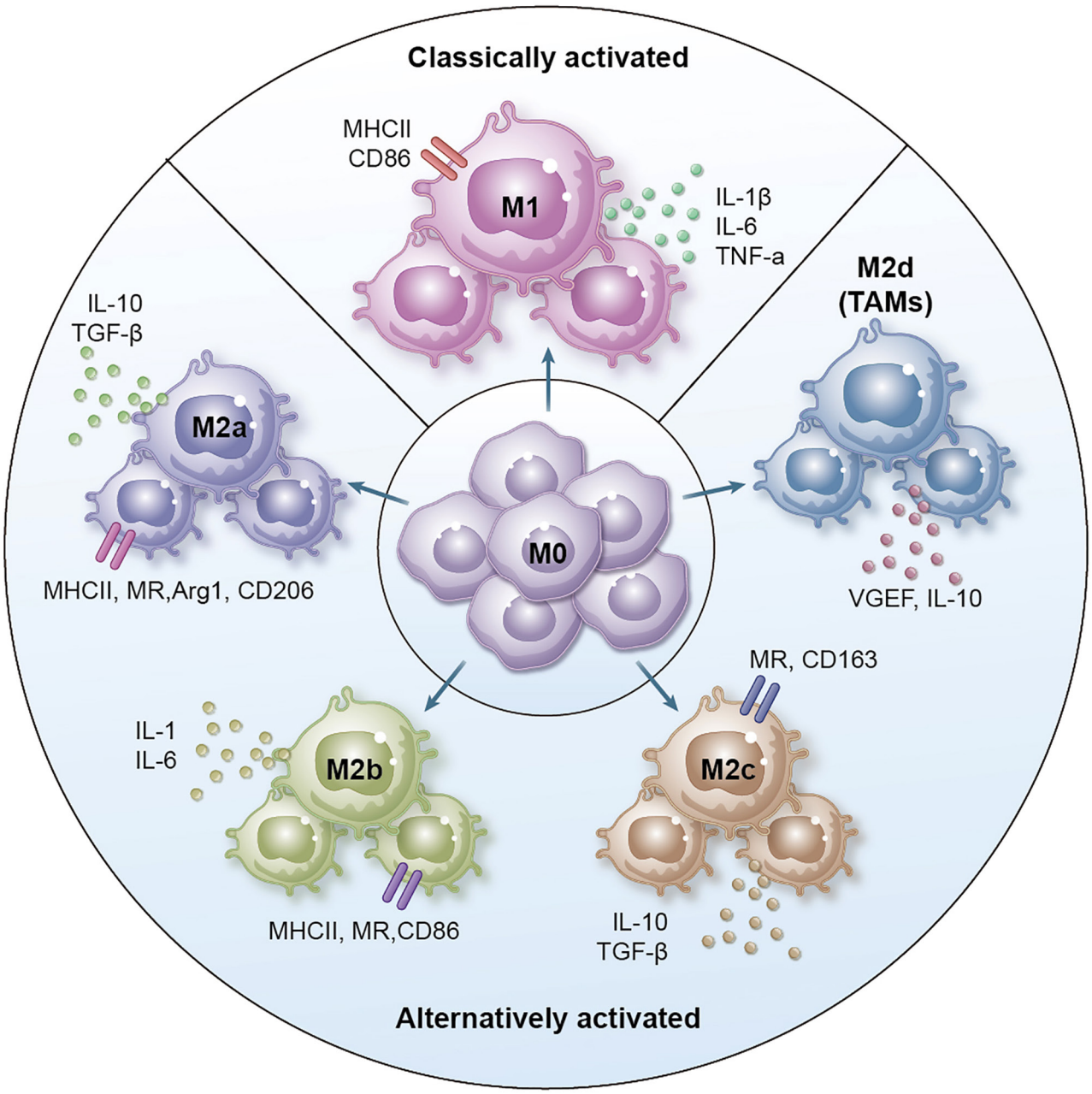


Figure S10. Effects of sepsis-induced M1/M2 macrophage polarization on the immune system. During sepsis, LPS exposure activates M1 macrophages via the TLR pathway, inducing the NF-κB signaling cascade and driving the production of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6. M1 macrophages also release substantial amounts of ROS, causing mitochondrial dysfunction and activating the cGAS-STING pathway, which results in intestinal inflammation. Additionally, M1 macrophages secrete TF, activating the exogenous coagulation system and leading to intestinal microvascular obstruction. Upregulated glycolysis through the HK2/PKM2 pathway increases lactate production and HIF-1α expression, further enhancing intestinal inflammation. LPS, lipopolysaccharide; TLR, Toll-like receptor; ROS, reactive oxygen species; cGAS, cyclic guanosine monophosphate-adenosine monophosphate synthase; STING, stimulator of interferon genes; TRIF, TIR-domain-containing adapter-inducing interferon-β; IRF3, Interferon regulatory factor 3; STAT3, Signal transducer and activator of transcription 3; TGF-β, Transforming growth factor beta; VEGF, Vascular endothelial growth factor; IL, Interleukin; TF, tissue factor; HIF-1α, hypoxia-inducible factor-1α; HK2, hexokinase 2; CD14, Cluster of Differentiation 14; MD2, Myeloid Differentiation Protein 2; M1, M1 macrophage; M2, M2 macrophage; PKM2, pyruvate kinase isoform M2; ZO-1, zonula occludens-1.

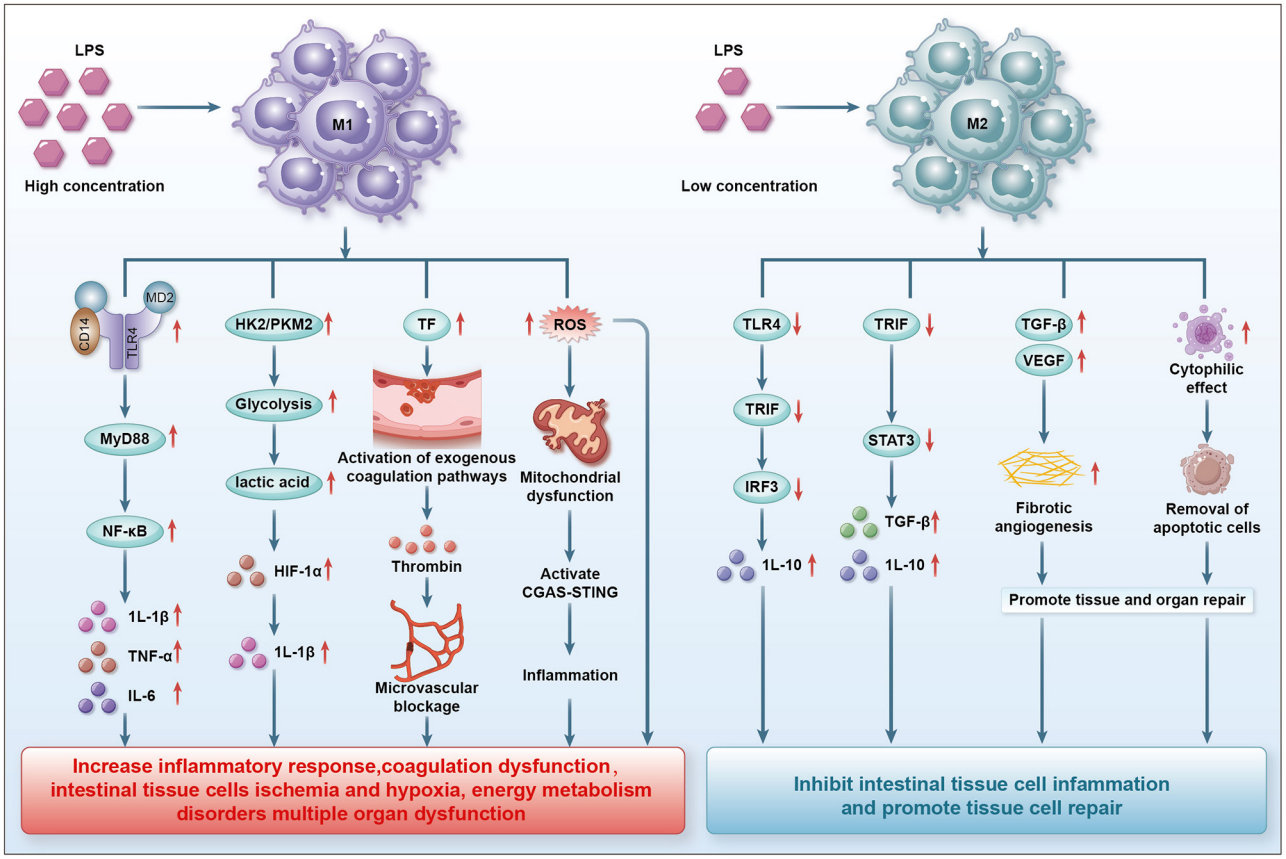


Figure S11. Pharmacological effects of resveratrol.

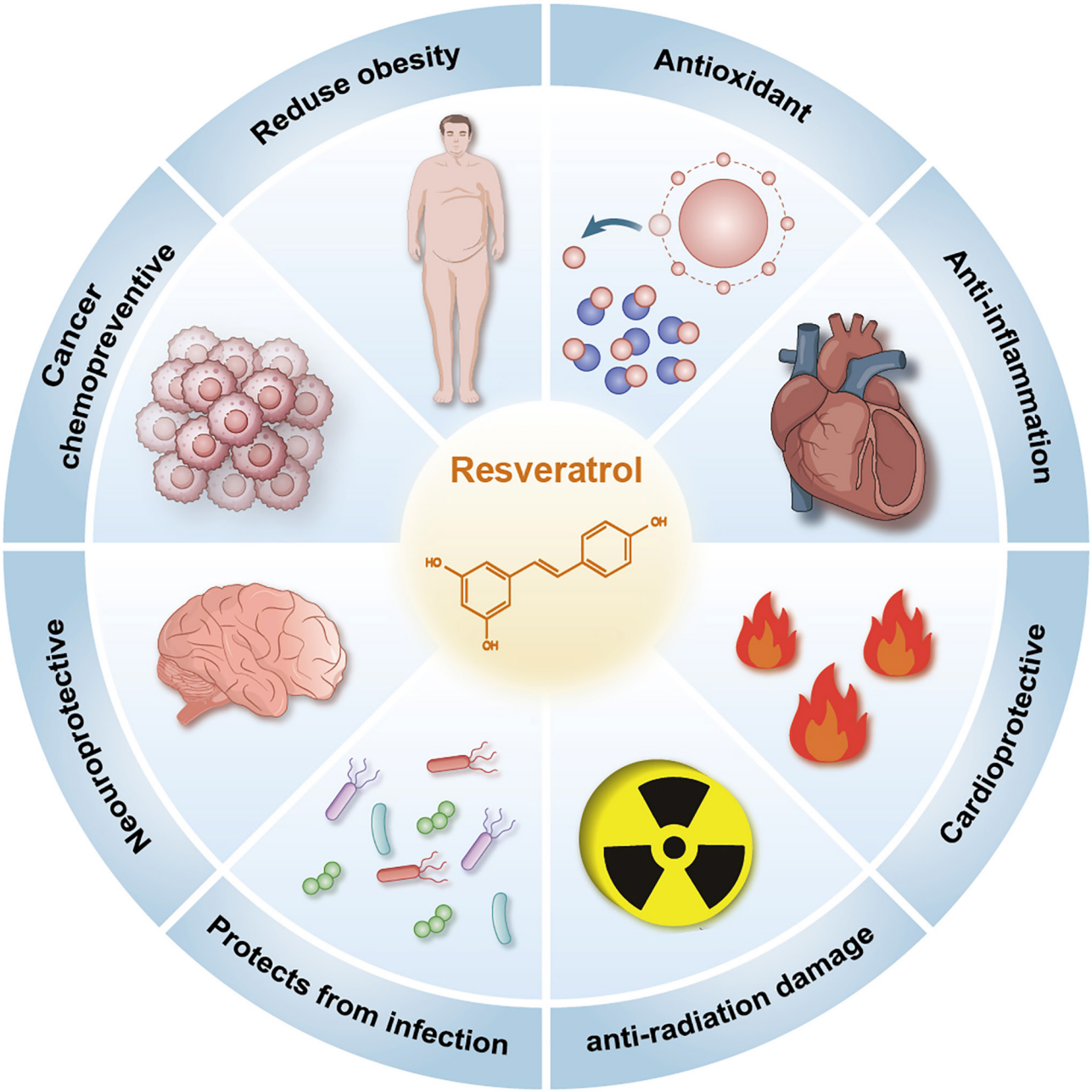


Figure S12. Mechanisms of macrophage-derived inflammatory mediators, oxidative stress, epithelial apoptosis, tight junction regulation and mucosal immune responses during sepsis and the mechanisms by which resveratrol may intervene in these processes. During sepsis, macrophage activation and neutrophil recruitment promote the release of inflammatory mediators and oxidative stress, inducing intestinal epithelial cell apoptosis, intestinal immune dysfunction and damage to intestinal tight junction proteins. Conversely, resveratrol inhibits macrophage activation and neutrophil recruitment, suppresses intestinal epithelial cell inflammation and oxidative stress, decreases intestinal epithelial cell apoptosis and improves intestinal immune function and intestinal tight junction protein function by regulating the TLR4/NF-κB, Nrf2/HO-1, PI3K/Akt and MLCK pathways. LPS, lipopolysaccharide; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; TLR4, Toll-like receptor 4; NF-κB, nuclear factor kappa B; ·OH, Hydroxyl radical; H_2O_2, Hydrogen peroxide; ONOO-, Peroxynitrite; Bax, BCL2-associated X protein; Bcl-2, B-cell lymphoma 2; ZO-1, Zonula occludens-1; MLCK, Myosin light chain kinase; Th1, T helper type 1 cell; Th17, T helper 17 cell; IFN-γ, Interferon gamma; Treg, Regulatory T cell; sIgA, Secretory immunoglobulin A; SOD, Superoxide dismutase; CAT, Catalase; GPx, Glutathione peroxidase; HO-1, Heme oxygenase-1; MAPK, Mitogen-activated protein kinase; TNF-α, Tumor necrosis factor alpha; IL, Interleukin; MCP-1, Monocyte chemoattractant protein-1; iNOS, Inducible nitric oxide synthase; COX-2, Cyclooxygenase-2; CXCL1, Chemokine (C-X-C motif) ligand 1; CXCL2, Chemokine (C-X-C motif) ligand 2; MODS, multiple organ dysfunction syndrome; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; SIRT1, sirtuin 1; PGE2, Prostaglandin E2; RNS, Reactive nitrogen species; LTB4, Leukotriene B4; NO, Nitric oxide; ROS, Reactive oxygen species.

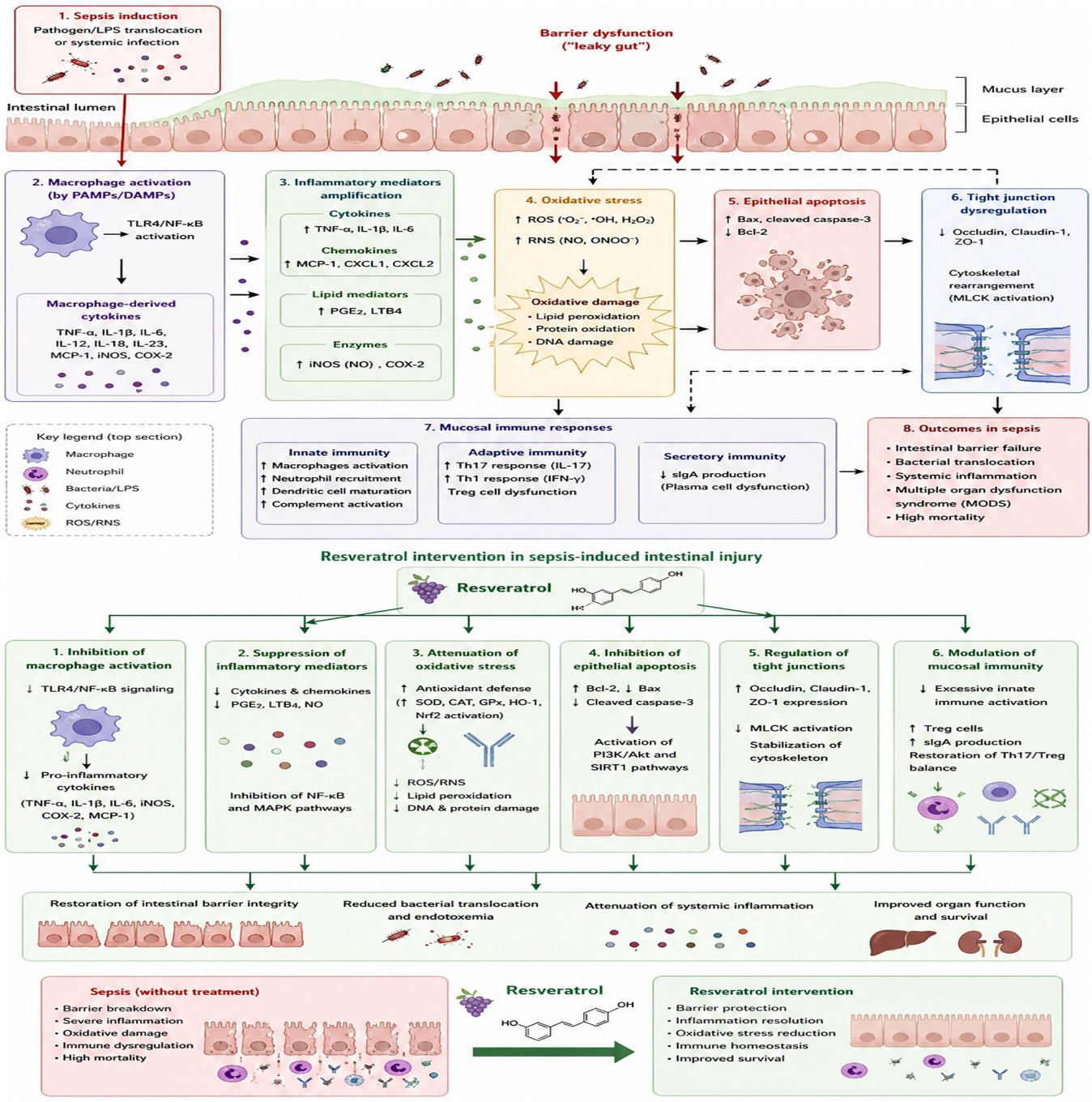


Figure S13. Effect of M1/M2 macrophage polarization on sepsis-induced intestinal injury. During sepsis, LPS and bacteria induce macrophage polarization toward the M1 phenotype, releasing TNF-α, IL-1β, IL-6, IL-12, iNOS, ROS and NO, inducing intestinal epithelial cell apoptosis, tight junction disruption and intestinal epithelial barrier injury. During the recovery period of sepsis or after treatment with resveratrol, M2 macrophage polarization participates in anti-inflammatory responses by releasing anti-inflammatory mediators such as IL-10, TGF-β and IL-1RA, inducing intestinal epithelial cell survival and proliferation, alleviating tight junction disruption and improving intestinal epithelial barrier injury. LPS, lipopolysaccharide; TNF, tumor necrosis factor; IL, interleukin; IFN-γ, Interferon gamma; ZO-1, Zonula occludens-1; M-CSF, Macrophage colony-stimulating factor; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; TGF-β, transforming growth factor beta; Arg1, arginase 1; FIZZ1, Found in Inflammatory Zone 1; GM-CSF, granulocyte-macrophage colony stimulating factor; M1, M1 macrophage; M2, M2 macrophage; Ym1, chitinase 3-like protein 3; STAT, signal transducer and activator of transcription; miR, microRNA; NO, nitric oxide; PPARγ, peroxisome proliferator-activated receptor gamma.

