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Review Article

Intestinal macrophages in pathogenesis and treatment of gut leakage: current strategies and future perspectives

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Abstract

Macrophages play key roles in tissue homeostasis, defense, disease, and repair. Macrophages are highly plastic and exhibit distinct functional phenotypes based on micro-environmental stimuli. In spite of several advancements in understanding macrophage biology and their different functional phenotypes in various physiological and pathological conditions, currently available treatment strategies targeting macrophages are limited. Macrophages' high plasticity and diverse functional roles—including tissue injury and wound healing mechanisms—mark them as potential targets to mine for efficient therapeutics to treat diseases. Despite mounting evidence on association of gut leakage with several extraintestinal diseases, there is no targeted standard therapy to treat gut leakage. Therefore, there is an urgent need to develop therapeutic strategies to treat this condition. Macrophages are the cells that play the largest role in interacting with the gut microbiota in the intestinal compartment and exert their intended functions in injury and repair mechanisms. In this review, we have summarized the current knowledge on the origins and phenotypes of macrophages. The specific role of macrophages in intestinal barrier function, their role in tissue repair mechanisms, and their association with gut microbiota are discussed. In addition, currently available therapies and the putative tissue repair mediators of macrophages for treating microbiota dysbiosis induced gut leakage are also discussed. The overall aim of this review is to convey the intense need to screen for microbiota induced macrophage-released prorepair mediators, which could lead to the identification of potential candidates that could be developed for treating the leaky gut and associated diseases.

Keywords: barrier damage, gut leakage, macrophages, microbiota, pathogenesis, tissue repair

1. Introduction

Macrophages were first described as phagocytes in 1882 by Élie Metchnikoff, and this cell type has been found residing in almost every tissue of the body as large, tissue-resident myeloid cells, characterized as having pseudopodia and phagocytic granules and by distinct functional profiles. As a central part of the innate immune system, they serve a crucial host defense function and contribute to the maintenance of tissue homeostasis by clearing apoptotic and damaged cells. Macrophages also play an essential role during organogenesis in embryonic development, in which they are highly concentrated at sites of high cell death, such as the developing limb buds.[1,2] These tissue remodeling functions are maintained in adults and support wound healing and tissue repair/remodeling processes after infection and injury. Macrophages can also acquire tissue-specific phenotypes and functions in different organs. Although they exert tissue-specific functions, all such tissue-specific macrophages also release common soluble mediators including enzymes, cytokines, chemokines, and arachidonic acid derivatives, as well as glycoproteins such as fibronectin, that help with the maintenance of homeostasis and tissue repair.[3,4]

2. Origin, differentiation and plasticity

After a decade of studies, the role of monocyte/macrophage functions was found to be dependent on the state of macrophage differentiation.[5,6] Re-established concepts in macrophage biology have led to a new understanding of the origins, biology, and phenotypes of lung macrophages. Mounting evidence in recent years has revealed the plasticity of macrophages and has indicated that macrophages may arise through differentiation through a precursor cell type (Fig. 1). Macrophages originate during the prenatal stage from the yolk sac and fetal liver and during the postnatal stage from the bone marrow.[7,8] Tissue-resident macrophages were shown to arise from embryonic progenitors that seed and mature locally before and shortly after birth. They are maintained by proliferative self-renewal mechanisms throughout life, largely independent of replenishment by blood monocytes in the steady state.[9–11] However, during inflammation, blood monocytes are recruited from the bone marrow to inflamed tissues where they differentiate into macrophage populations. These macrophages can be polarized into wide spectrum of functional phenotypes based on the microenvironmental stimuli; however, to simplify, they are broadly classified into an proinflammatory M1 and anti-inflammatory M2 phenotypes.[12] M1 macrophages are usually identified with the expression of major histocompatibility complex class II, CD80, CD86, and CD16/32. They usually secrete proinflammatory cytokines like tumor necrosis factor (TNF), interleukin (IL)-6, IL-12, and the chemokines CXCL9, CXCL10, and CXCL11. These cytokines are essential for clearing infections but they can also promote tissue injury. In contrast, M2 macrophages are identified

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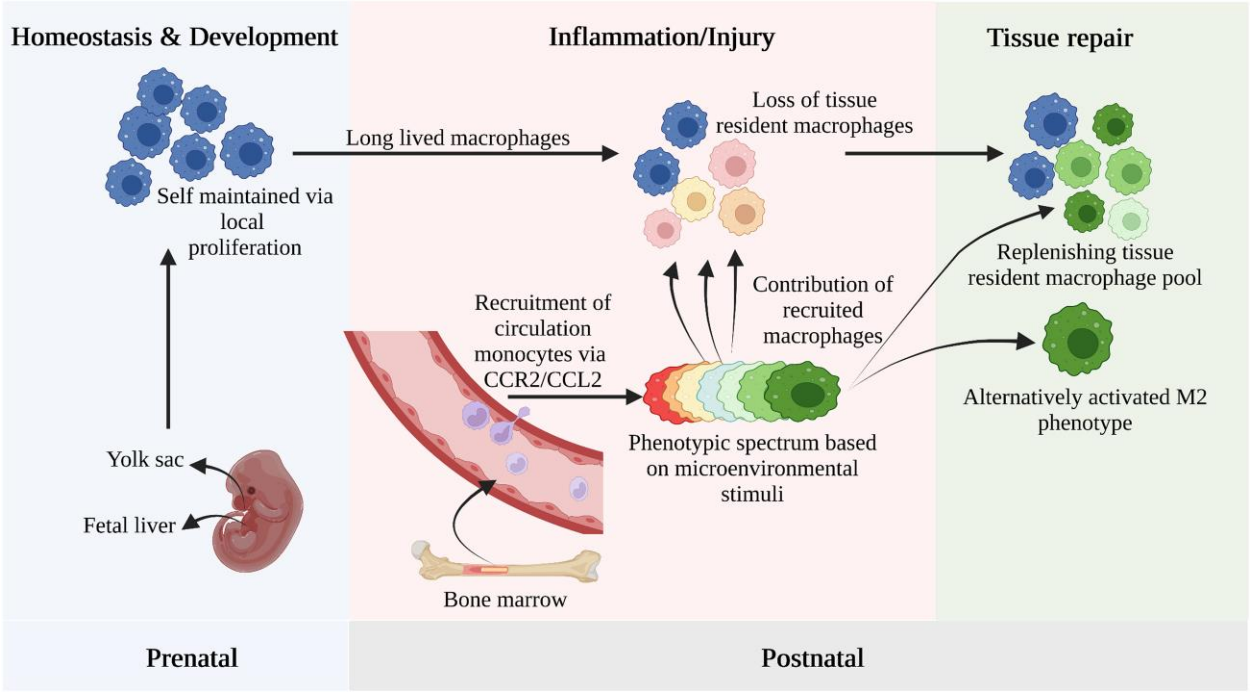

Fig. 1. Macrophage origin, differentiation, and plasticity. Macrophages may originate both at the prenatal stage from the yolk sac and fetal liver and during the postnatal stage from the bone marrow via the CCL2/CCR2 axis. In specific tissue contexts, macrophages are programmed by local factors. Here they may be both long-lived self-renewing cells or replenished from the blood monocyte pool. The macrophage activation states in tissues can be loosely equated to macrophages in disease tissues, but they are heterogeneous in origin and phenotypically plastic, with variable contributions to disease progression. They show an alternatively activated M2 phenotype in the repair phase and could substitute the tissue resident macrophages. Created with BioRender.com.

with high expression of mannose receptor (CD206) and hemoglobin receptor (CD163). They can secrete anti-inflammatory factors like arginase-1, IL-10, and chemokines CCL17 and CCL22. These mediators mediate antiparasitic actions and promote tissue repair and remodeling mechanisms. However, still their distinct functional responses and reprogramming mechanisms are largely unexplored especially in intestinal compartments.

Tissue-resident macrophages originate from both the yolk sac and fetal liver in the prenatal stage. During inflammation/injury, an additional subset of macrophages originate from the bone marrow and migrate into inflamed tissues.[13] These infiltrated macrophages require predominantly CCL2/CCR2 axis, which was evidenced in CCR2 knockout (KO) mice that showed deficit monocyte infiltration into gut tissues.[14,15] These infiltrated macrophages are exposed to the micro-environmental stimuli and correspondingly adapt their functional repertoire, and differentiate into tissue resident macrophages, if these are depleted, by inflammatory stimuli or by infection.[16]

In mice, 2 blood monocyte subsets have been distinguished based on the differential expression of Ly6C and CX_3CR1.[17] Monocytes that express high Ly6C levels and intermediate CX_3CR1 levels are termed $Ly6C^{hi}$ monocytes. They are also known as inflammatory monocytes due to their ability to migrate to sites of inflammation and produce proinflammatory cytokines during infection or tissue damage.[17,18] The second major monocyte subset in mice characterized by low Ly6C expression, high CX_3CR1 expression, and low CCR2 expression is termed the $Ly6C^{low}$ subset, which patrols for monocytes, acting to maintain capillary integrity.[19] After extravasation, $Ly6C^{hi}$ monocytes differentiate into macrophages and monocyte-derived dendritic cells. Despite resident macrophages longevity and self-renewing property during homeostasis,[20] infiltrated macrophages ($CD11c^{low}CD11b^{hi}$) from circulating blood $Ly6C^{hi}$ monocytes can complement the prenatally established macrophage compartment, especially under severe inflammatory conditions such as irradiation and infection that cause severe depletion of the resident macrophage population.[21] During later stages of injury, long-lived self-renewing resident macrophages can also help in replenishing the resident pool. Thus, resident macrophages may have a chimeric origin, being derived from both yolk sac/fetal liver as well as from bone marrow monocytes.[22–24] In addition, the distinct functions of resident and recruited macrophages suggests that these were well classified based on their origins.[25] Moreover, several experiments as far back as the early 1970s established that the influx of macrophages plays a crucial role in tissue repair.[26,27] Peripheral blood monocytes can also replenish tissue macrophages through mechanisms dependent on granulocyte-macrophage colony-stimulating factor and colony-stimulating factor 1 signaling in a stimulus-specific manner.[28] Later, these macrophage subsets were classified as alternatively activated macrophages,[29] which were found to be involved in development, repair, and tissue homeostasis processes.[30]

3. Intestinal macrophage phenotypes

Gut-resident macrophages do not fit readily into this M1-M2 paradigm, having some of hallmarks of both M1 and M2 macrophages.[28] For instance, they express high levels of major histocompatibility complex class II and produce TNF-α constitutively, features normally associated with M1 or classically activated macrophages. However, they also express CD206, CD163, and produce IL-10, features associated with M2 or M2-like macrophages.[2] However, they fail to express arginase, which is a key feature of M2 macrophages. Thus, like most tissue macrophages in vivo, those resident in the gut wall adapt to their local environment in complex and specific ways that may not be reflected by the rigid classification of the M1-M2 paradigm.

Table 1. Intestinal macrophage phenotype markers in health and disease.

	Mice	Human
Healthy	Surface markers: CD11b^{+}, F4/80^{+}, CD64^{+}, CD68^{+}, MHCII^{+}, CD11c^{low}, CD103^{+}, MERTK^{+}, CX3CR1^{hi}, CD163^{+}, and CD206^{+}Tim4^{+}CD4^{+} (long lived) Secreted markers: IL-4, IL-13, IL-10, TGFβ, GM-CSF, Arg-1, Relm, and Chil3[9,34,37–40]	Surface markers: CD11b^{+}, CD64^{+}, CD68^{+}, CD11c^{low}, HLA-DR^{+}, CX3CR1^{hi}, CD163^{+}, and CD206^{+} Secreted markers: TGFβ, IL-10, and GM-CSF[33,39–41]
IBD (UC and CD)	Surface markers: CD14^{hi}, Ly6C^{hi}, CD11b^{+}, F4/80^{+}, CD68^{+}, CD11c^{+}, MHCII^{+}, CX3CR1^{int}, and CD86^{+} Secreted markers: TNF-α, iNOS, IL-1β, IL-12, IL-23, IL-1, IL-6, MCP-1, CCL3, CCL4, CCL5, CCL8, and CCL11[34,41–45]	Surface markers: CD14^{hi}, CCR2+, CD11c^{hi}, CD68^{+}, CD80^{+}, CD86^{+}, and CD40^{+} Secreted markers: TNF-α, IL-6, IL-1β, iNOS, and TREM-1[31–35,40,41,46]
Chronic IBD (ulcerative colitis and CD)		Surface markers: CD68^{+}, CD206^{+} Secreted markers: TNF-α, IL-13, MMP2, and TGFβ[47]
Parasite infection	Surface markers: CD11b^{+}, F4/80^{+}, CD68^{+}, CD62L^{+}, TGFBR2^{+}, CD11c^{+}, MHCII^{+}, CD206^{+}, and CD163^{+} Secreted markers: Fizz-1, Arg-1, Chil-1, HO-1, and IGF[40,48–50]	Surface markers: CD11b^{+}, CD68^{+}, HLA-DR^{+}, and CD206^{+}[40,49]
Aging	Secreted markers: IL-6, TNF-α, IL-1β, and iNOS[51,52]	
Antibiotic-induced dysbiosis	Surface markers: Ly6C^{+}, CD11b^{+}, F4/80^{+}, MHCII^{+}, and CX$_3$CR1^{+} Secreted markers: TNF-α, IL-6 and MCP-1, Arg-1, Chi3l3, and Retnla[53–55]	

Abbreviations: Arg-1 = arginase-1; GM-CSF = granulocyte-macrophage colony-stimulating factor; IGF = insulin-like growth factor; MHC = major histocompatibility complex; MMP = matrix metalloproteinase.

An increased number of classically activated macrophages characterized with CD14^{hi}HLA-DR^{low} and CD40^{hi} subset are observed in the mucosal compartment of patients with Crohn's disease (CD).[31,32] In addition, intestinal macrophages characterized with the expression of CD11c^{hi}CCR2^{hi}CX3CR1^{hi} and endogenous proinflammatory markers TNF-α, IL-1β, IL-6, and inducible nitric oxide synthase (iNOS) damage the intestinal epithelial barrier and play an important role in the development of inflammatory bowel disease (IBD).[33,34] Furthermore, gut infiltrated macrophages with iNOS and TNF-α expression can reduce the transepithelial resistance, deregulate tight junction proteins, and promote intestinal epithelial cell apoptosis.[35] Moreover, a decreased production of IL-10 in mucosal macrophages are speculated to impair the integrity of intestinal mucosal barrier.[36] Mouse and human intestinal macrophages markers are conserved; however, markers like CD64; proto-oncogene, Mer tyrosine kinase (MERTK); Tim4; and CD4 differ in their expressions between species and disease conditions (Table 1). Intestinal macrophage populations can be distinguished from dendritic cells by the expression of CD64 and CD14.[34] In addition, considering that the intestinal macrophage phenotypes are not readily falling under classic M1 and M2 phenotypes, intestine-specific lineage markers like CX3CR1$^{hi/int}$ and more than one costimulatory or scavenging receptor must be used to validate the phenotype of these macrophages. Moreover, intestinal macrophage phenotypes in other disease conditions associated with gut leakage like obesity, metabolic diseases, asthma, allergies, and neurological diseases and intestinal macrophage phenotypes in other health conditions like aging, antibiotics use, diet, and unhealthy lifestyle are not yet well characterized. Therefore, further studies are required to understand their specific functional phenotypes in different disease conditions in context of gut leakage and local microbiota niches.

4. Gut leakage

Emerging studies have showed different causes of gut leakage (Fig. 2); however, altered gut microbiota (dysbiosis) is the underlying fundamental cause in all conditions. The intestinal epithelium, which is mainly made up of a single layer of intestinal cells, is tightly connected with adjacent cells to form a critical, continuous physical barrier assisted by tight junction proteins, which regulates the selective permeability of luminal content.[56,57] The assembly of intestinal epithelial tight junctions is regulated by claudins, occludins, zonula occludens, and actins. Disruption of this epithelial barrier increases intestinal permeability, resulting in leaky gut syndrome: an acute inflammatory condition characterized by functional and structural losses and disruption of epithelial integrity the basement membrane, which leads to the efflux of bacterial toxins and other proinflammatory mediators into systemic circulation.[58] During intestinal epithelial cell injury, loss of tight junction integrity and apoptosis drive increased permeability and, in severe cases, eventually to a denuded basement membrane. During microbial dysbiosis, unfavorable inflammatory cascades are activated in the gut lumen that trigger the proinflammatory cytokine storm leading to intestinal epithelial membrane damage. Despite increasing insights into disease pathogenesis from experimental and clinical studies, dysbiosis remains a leading cause of several diseases among patients in critical care, with multiorgan failure and increasing mortality rates.[59] Increasingly, the body of evidence implies a link between dysbiosis-induced intestinal barrier dysfunction and development of several pathogenic conditions such as IBD,[60] obesity,[61] bone diseases,[60] liver diseases,[62] autoimmune diseases,[63] and neuroinflammation.[58] Intestinal pathobionts are observed to be increased in patients with inflammatory disorders, where they accelerate systemic inflammation by translocating across the epithelial barrier to reach extraintestinal tissue (Fig. 2). Other periodontopathic bacteria like *Porphyromonas gingivalis* and *Fusobacterium nucleatum* can induce gut dysbiosis and damage epithelial cells.[64,65] In addition, there are several factors that can influence gut leakage via modulating gut microbiota including antibiotics, stress, smoking, infection, diet, and diseases. During gut epithelial barrier damage, several proteins are released in the systemic circulation, such as zonulin, lipopolysaccharide-binding protein, soluble CD14, and intestinal fatty acid binding protein, and these are used as biomarkers for gut leakage both clinically and experimentaly.[66,67] Macrophages, being a predominant immune cell population in the intestine, might have an

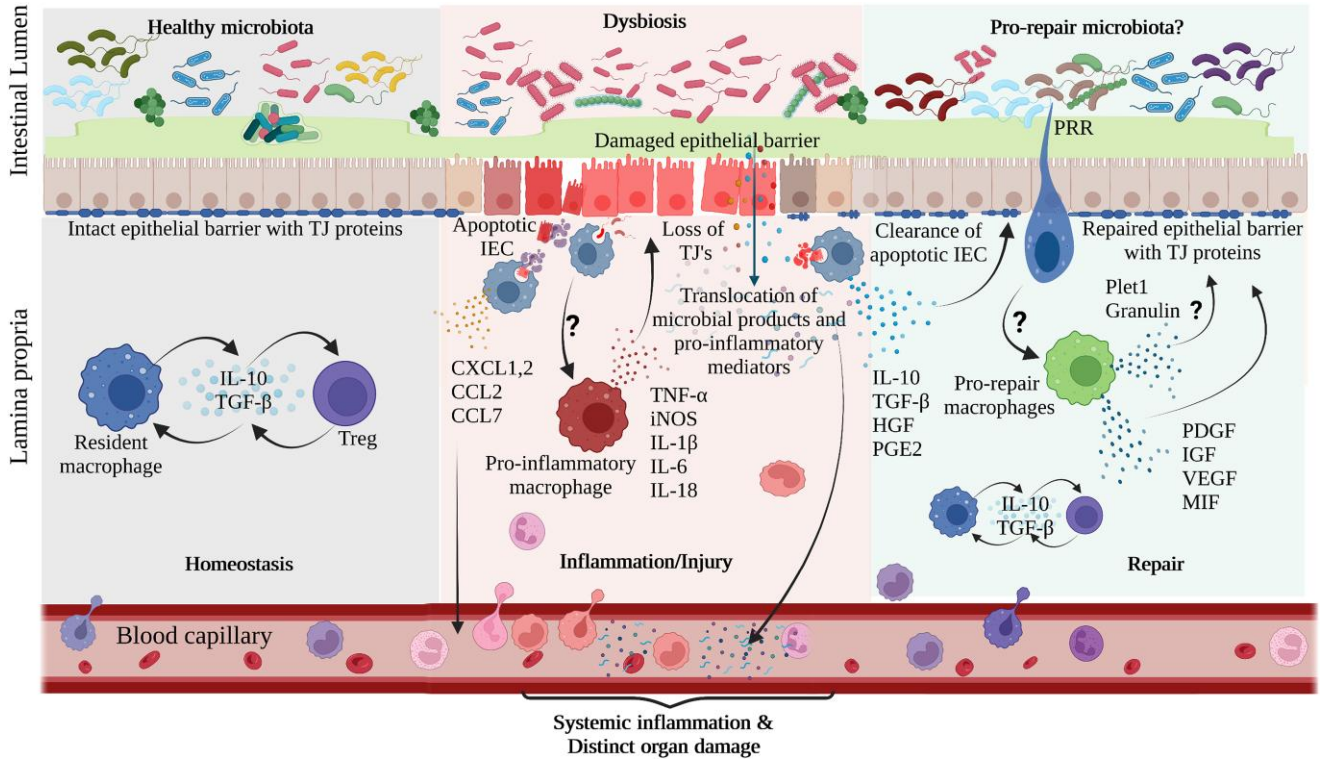

Fig. 2. The role of macrophages in association with microbiota in maintaining intestinal barrier function. During homeostasis in the lamina propria, crosstalk between resident intestinal macrophages and regulatory T cells (Treg) results in IL-10 and TGF-β production that helps to maintain the intact intestinal epithelial cell (IEC) barrier with tight junction (TJ) proteins. The intestinal lumen is mainly populated with healthy microbiota in homeostasis. In disease conditions, intestinal recruited macrophages show a proinflammatory phenotype with the release of TNF-α, iNOS, IL-1β, IL-6, and IL-18, which further damages the IEC barrier. However, if this acquired phenotype is due to phagocytosis of specific dysbiotic microbial products is yet to be studied. In addition, macrophages that phagocytose apoptotic IECs release chemokines like CL2, CCL7, CXCL1, and CXCL2, which recruits further neutrophils and monocytes into intestinal tissues. At this phase, the intestinal lumen observed with dysbiosis, apoptotic IECs, and a damaged IEC barrier with loss of TJ proteins leads to translocation of microbial products and proinflammatory mediators into the lamina propria and eventually to systemic circulation promoting systemic inflammation and distinct organ damage. During the repair phase, macrophages acquire a prorepair phenotype and release various tissue repair mediators including TGF-β, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), and IL-10 along with proposed repair mediators like Granulin and Plet1. These mediators resolve the inflammation and repair IEC barrier by expression of TJ proteins and regulate the intestinal barrier function. However, if this acquired phenotype is due to phagocytosis of specific prorepair microbial products is yet to be studied. HGF = hepatocyte growth factor; MIF = macrophage migration inhibitory factor; PRR = pattern recognition receptor. Created with BioRender.com.

potential role in gut leakage. An increased number of activated macrophages are observed in the mucosal compartment of patients with intestinal inflammatory disorder.[31,32] In addition, intestinal macrophages characterized with the expression of proinflammatory markers TNF-α, IL-1β, IL-6, and iNOS damage the intestinal epithelial barrier and play an important role in the development of IBD.[33,34] However, the direct role of these macrophages in the induction of gut leakage is not well understood. To date, no satisfactory, specific treatments have been developed to treat leaky gut syndrome. Moreover, several probiotic agents from successful trials, showing promise in both experimental and preclinical studies, failed to show an overall improvement in mortality during clinical trials, due to adverse effects and unfavorable alterations in the gut microbiota.[68] Therefore, there is an urgent medical need for the development of novel therapies to further improve clinical outcomes.

5. Macrophages in regulating intestinal barrier function

Intestinal macrophages play a key role in the gut immune system and the regulation of gastrointestinal physiology, including gut motility and secretion. In homeostatic conditions, macrophages are one of the most abundant intestinal immune cells. Intestinal macrophages inhabit the lamina propria and are involved in a variety of biological processes, including removal and degradation of microorganisms and tissue repair.[48,69] Intestinal macrophages also limit inflammation, facilitate the survival of local FOXP3+ T regulatory cells, and maintain epithelial integrity.[70,71] Intestinal macrophages localize closely with epithelial cells and disruption of this association results in loss of intestinal barrier function, as reported in IBD such as ulcerative colitis (UC) and CD.[72] Both epithelial and macrophage protein tyrosine phosphatase nonreceptor type 2 is found to have an important role in facilitating the association of intestinal epithelial cells with macrophages to maintain intestinal barrier function.[73] However, the mechanisms by which macrophages regulate intestinal epithelial barrier function need further validation. One of possible mechanisms could be the intestinal macrophage-microbiota crosstalk. Intestinal macrophages take advantage of the close proximity with gut microbiota to access and probe microbes and their components by 2 major pattern recognition receptors: (1) scavenger receptors and (2) toll-like receptors (TLRs). Class A1 scavenger receptor (SR-A1) or macrophage scavenger receptors are observed to regulate intestinal barrier function in IBD. Both in vitro and in vivo studies using transgenic SR-A1–deficient mice and blocking antibodies

demonstrated an anti-inflammatory effect of SR-A1 associated with reduced M1 phenotype and clonic epithelial apoptosis, by which it could protect the intestinal barrier function.[36,74] Similarly, TLR signaling upon gut microbial interaction can generate multiple defense mechanisms including tight junction protein expression, antimicrobial peptide production, and mucus production.[75] Moreover, TLR2 and TLR4 activation by commensal gut bacteria can increase transepithelial resistance and an increase in intestinal epithelial cell survival via upregulation of connexin 43 (a key protein involved in gap junctional intercellular communication). In addition, TLR4 can promote crosstalk between intestinal epithelial cells and macrophages, leading to increased expression of IL-10 in the epithelial barrier, which is important in maintaining intestinal barrier function.[75] A proinflammatory cytokine storm drives the recruitment of monocytes that polarize to a proinflammatory macrophages in intestinal tissues and release proinflammatory cytokines like tumor necrosis factor α (TNF-α), interleukin (IL)-6, IL-1β, and NO, which contributes to the disruption of intestinal barrier function.[76] Pathogens cross the damaged intestinal epithelial cell barrier and stimulate macrophages to produce more proinflammatory cytokines, such as IL-1, IL-6, IL-18, and TNF-α. These act on intestinal epithelial cells directly or indirectly, leading to the injury or necrosis or apoptosis of intestinal epithelial cells, disruption of the epithelial barrier, and deregulation of tight junction proteins, as observed in IBD.[33] Similarly, macrophage exposure to lipids from a high-fat diet restricted the uptake of apoptotic cells and induction of IL-10.[77] This results in poor intestinal barrier repair and continued intestinal injury leading to gut leakage. Despite there being few available studies on the role of macrophages in upregulating tight junction proteins, macrophage-released mediators like macrophage inhibitory factor and its receptor CD74 have been reported to play a major role in the maintenance of the intestinal barrier function.[78,79] In a recent study, the subepithelial macrophages protected the distal colon epithelial cells from hazardous luminal fungal metabolites, thereby preventing gut leakage and maintaining the barrier function. In the absence of these macrophages, dysregulated intake of fungal products by the epithelial cells lead to apoptosis and subsequent loss of epithelial barrier integrity.[70] This study speculated that intestinal macrophages and their association with intestinal epithelial cells play a significant role in maintaining the barrier function. However, there is more to explore, to improve our understanding regarding the coordination between macrophages and epithelial cells in maintaining the intestinal barrier function. For example, whether the epithelial barrier damage drives intestinal macrophages into a proinflammatory state or proinflammatory macrophage phenotypes based on differential pathogen-associated molecular pattern molecule signals damage the epithelial barrier is still a matter of debate, and may depend on the nature of the gut microbiota composition. Therefore, the axis of gut microbiota-macrophage-epithelial barrier needs further extensive research to understand the pathology and treatment of various diseases associated with gut leakage.

6. Macrophages in tissue repair and regeneration

Macrophages represent the first line of defense in their resident tissues and serve as a unique leukocyte population by actively coordinating homeostasis, defense mechanisms, and resolution of inflammation. Macrophages are an important source of chemokines, matrix metalloproteinases, and other inflammatory mediators that drive the initial cellular response following injury.[80] After the early inflammatory phase subsides, the predominant macrophage population polarizes to a wound healing phenotype (i.e. characterized by the production of numerous growth factors including platelet-derived growth factor, transforming growth factor β1 [TGF-β1], insulin-like growth factor 1, and vascular endothelial growth factor α) that promotes cellular proliferation, mucosal wound healing, and blood vessel development.[80–82] They also produce soluble mediators that stimulate local and recruited tissue fibroblasts to differentiate into myofibroblasts, which facilitate wound contraction and closure as well as the synthesis of extracellular matrix components.[80] The proliferation and expansion of neighboring parenchymal and stromal cells are also regulated by macrophages, and if the injury is severe, macrophages can also activate additional stem cell and local progenitor cell populations that participate in repair. Thereafter, monocytes and/or macrophages exhibiting a mostly anti-inflammatory phenotype become the dominant population.[80] Macrophages respond to and secrete IL-10, TGF-β, and other inhibitory mediators, including cell surface receptors like PD-L1 and PD-L2 that play a major role in the tissue repair process.[80,83] Both clinical and in vivo studies have shown an association of early onset of IBD with IL-10 or IL-10 receptor mutations in intestinal chemokine receptor CX3CR1^{hi} resident macrophages. These data demonstrate that macrophage-derived IL-10 is dispensable for gut homeostasis.[71] Moreover, several studies have observed the role of macrophages in regeneration, wound closure, angiogenesis, and clearance of dead and aged cells.[81,84] Therefore, elucidating the mechanisms by which macrophages promote tissue regeneration at a requisite micro-environment may divulge strategies for the regeneration of injured organs.

Mounting evidence suggest different monocyte and macrophage populations possess distinct and nonredundant roles in tissue repair, fibrosis, and regeneration.[25] The mechanisms that instruct macrophages to adopt proinflammatory, pro–wound healing, profibrotic, anti-inflammatory, anti-fibrotic, proresolving, and tissue regenerating properties in various organ systems is not well understood.[85] Although effective wound repair and tissue regeneration is often associated with the preferential expansion of local tissue macrophages exhibiting an anti-inflammatory phenotype, when the injury is locally severe or chronic, additional inflammatory monocytes may also be required to restore normal tissue architecture. Nevertheless, the rapid conversion of these proinflammatory TNF-α producing macrophages to an anti-inflammatory IL-10 and TGF-β producing phenotype appears to be critical to the long-term survival of stem and progenitor cell populations in most tissues.[86] Thus, to facilitate effective organ regeneration and prevent fibrosis, the monocyte and macrophage response must be finely tuned.

Macrophage secreted tissue repair mediators, like TGF-β, IL-10, and IL-23, which are essential for the remodeling phase of wound healing, can be directed to treat gut leakage (Table 2). Further IL-33, IL-4 and IL-13 from macrophages are found to be capable of activating wound healing macrophages.[111] In addition, macrophages expressed TREM2,[112] granulocyte-macrophage colony-stimulating factor,[113] and emerging prorepair mediators like Granulin[114] and Plet1,[115] a wound repair mediator, have been recently shown to be expressed by resident alveolar macrophages and intestinal dendritic cells.[116,117] Moreover, a deficiency of intestinal macrophages may increase susceptibility to infection and inhibit the activity of tissue repair. These studies suggest a promising role of these proteins as therapeutic agents to treat gut inflammation and gut leakage. However, the mode of delivery and mechanism of action has to be carefully considered during

Table 2. Putative macrophage tissue repair mediators to treat gut leakage.

Mediator(s)	Function(s)	Reference(s)
TGF-β	Reduce inflammation, induce pathological structural changes, and induce anti-inflammatory repair phenotype.	82,87,88
PDGF	Enhanced the cascade of tissue repair processes required for a wound healing in vitro intestinal wound healing model.	87,89,90
IGF-1	Promoted the intestinal regenerative response after irradiation injury.	82,88,91
FGF-10	Enhanced signaling through the Fgfr2b receptor accelerated the repair process after gut injury.	92
Maresin and, resolvin-1	Secretory proteins proresolving lipid mediators and pathways are involved in resolution phase of inflammation.	93,94
MIF and its receptor CD74	Enhanced intestinal epithelial cell regeneration, healing, and maintaining mucosal barrier integrity.	79
ICAM-1	Role in macrophage efferocytosis and wound healing.	95
MMP-10	Extracellular matrix–degrading enzymes and moderating scar formation during wound repair were demonstrated.	96
IL-33[a]	Enhanced activation of wound healing macrophages.	96
IL-1ra	Enhance the messenger RNA expression of COX-2, iNOS, CINC-1, HGF, and bFGF, thereby contributing to gastric ulcer healing in vivo.	97,98
IL-10[a]	Reduces inflammation, induces pathological structural changes, and induce anti-inflammatory repair phenotype.	99,100
miRNAs let-7c, miR-124, and miR-223	Reported to promote M2 macrophage polarization and suppress M1 polarization.	101,102
miR-155	Central role in alternative M2 skewing in cardiac injury and colitis.	103,104
M2 macrophage–derived exosome miR-590–3p	Reduced colonic inflammation, strengthening mucosal healing, elevated survival in dextran sulfate sodium–induced colitis in mice and in radiation-induced gastrointestinal syndrome.	105,106
sTREM2	Enhances M2 phenotype and preserves macrophage pool after inflammatory insults.	107
Lysophosphatidic acid and Sphingosine 1-phosphate	Role in monocyte–macrophage system during wound healing and formation of atherosclerosis.	108,109
COX2	Potentiates efferocytosis and facilitates macrophage intestinal epithelial repair capacity.	110
Exosomes TGF-β, IGF-1, and VEGF	Reduces intestinal inflammation and enhances tissue repair, which represents an innovative treatment of IBD.	82

Abbreviations: bFGF = basic fibroblast growth factor; FGF = fibroblast growth factor; HGF = hepatocyte growth factor; ICAM = intercellular adhesion molecule; IGF-1 = insulin-like growth factor 1; iNOS = inducible nitric oxide synthase; MIF = macrophage migration inhibitory factor; miRNA = microRNA; MMP = matrix metalloproteinase; PDGF = platelet-derived growth factor; VEGF, vascular endothelial growth factor.
[a]Secreted molecules.

investigations. Taken together, macrophages are crucially involved in many aspects of wound healing. Depending on their polarization and the phase of wound healing, they may promote wound closure. Identifying mechanisms that support repair and understanding how these pathways are dysregulated in disease are key to improving resolution of intestinal tissue damage during gut leakage. Furthermore, epithelial repair during the proliferative phase may result in the complete restoration of gut barrier function. However, a dysregulated re-epithelialization frequently results in progression to the fibrotic phase of UC. Therefore, the associations of macrophage with epithelial cells in context of intestinal epithelial barrier repair needs to be carefully considered for future studies.

7. Interplay between intestinal macrophages and microbiota

Macrophages form a well-established cell type of the innate immune system that probe the host or invading microbes using pattern recognition receptors and exhibit efficient phagocytic and bactericidal activity.[118] Studies using germ-free or gnotobiotic mice models reported the potential role of gut microbiota in modulating macrophage phenotypes in the colon. Emerging studies have demonstrated the functional association of macrophages and gut microbiota that might be crucial to further understand and treat several diseases associated with gut dysbiosis–induced leaky gut syndrome. Despite the association of proinflammatory and anti-inflammatory macrophage phenotype in intestinal inflammatory and repair conditions respectively,[119] the role of specific bacterial species on modulating macrophage phenotype is less studied. For example, bacteria such as *Enterococcus faecalis* polarize colonic macrophages toward the proinflammatory phenotype in IL10 transgenic mice validate with the expression of cellular proteins (iNOS and arginase) by immunohistochemistry.[120] In addition, few studies have demonstrated an indirect association of dysbiosis with proinflammatory phenotypes. For example, antibiotics induced dysbiosis with reduced Firmicutes and Bacteroidetes and decreased fecal concentrations of short-chain fatty acids have been associated with the accumulation of proinflammatory macrophages.[121] In contrast, *Clostridium butyricum* directly induced IL-10 production by intestinal macrophages in inflamed mucosa and triggered polarization of the macrophages into the anti-inflammatory phenotype through the TLR-2/MyD88 pathway.[122] In addition, *Bacteroides fragilis* and Clostridia class, *F. nucleatum* induce M2 polarization based on the surface expression of CD206 in vitro and in vivo.[123] *Lactobacillus intestinalis* and *L. johnsonii* improved mercury-induced injury and intestinal permeability in vitro by promoting epithelial cell wound healing in a bicameral model consisting of Caco-2 and HT29-MTX intestinal epithelial cells and THP-1–derived macrophages..[124] *L. johnsonii* alleviates colitis via promoting the surface expression of CD206 on macrophages and release of IL10.[125] *Mytilus coruscus* reduced proinflammatory cytokines from macrophages in vitro and increased the abundance of some probiotics like *Anaerotruncus*, *Lactobacillus*, *Desulfovibrio*, *Alistipe*, *Odoribacter*, and *Enterorhabdus* in the colon and improved intestinal barrier integrity in vivo.[126] In addition, colonization of *Lactobacillus* species in mice and organoid models was observed to drive macrophage polarization toward an anti-inflammatory phenotype with the expression of CD206 and secreted Wnt ligands that subsequently

promoted stem cell differentiation.[127] Interestingly, an in vivo study demonstrated the depletion of macrophages alters bacterial gut microbiota by promoting fungal overgrowth.[128] In contrast, a normal gut microbiota was essential to drive macrophage-dependent intestinal stem cell self-renewal mechanisms.[129] Moreover, microbial metabolites also have been studied in intestinal epithelial barrier repair via modulating macrophages. For example, butyrate, docosahexaenoic acid, and other short-chain fatty acids reduce inflammation and help repair the intestinal barrier by macrophages with increased expressions of CD206 and arginase-1 driven by H3K9/STAT6 signaling pathway.[130–132] In addition, bacterial components such as lipopolysaccharides and flagellin are reported to modulate and activate M2 macrophages represented by IL-3 and TGF-β signaling.[133] Macrophages infected by *F. nucleatum* upregulate IDO on the cell surface, suggesting an additional mechanism whereby *F. nucleatum* might trigger macrophage-driven immunosuppression.[134] However, the vast majority of these studies relied on a specific microbial interaction with the macrophages in contrast to the real situation, in which a spectrum of microbial dysbiosis is observed in the specific diseases. In future, the disease-specific microbial dysbiosis has to be considered to understand the functional phenotype of macrophages. Further, these studies suggest that an explicit association of macrophages and gut microbiota and a careful modulation of microbiota composition might trigger a favorable macrophage phenotype to treat different disease conditions. In addition, gut microbiota (commensal bacteria)–trained macrophages may be a useful tool to treat gut leakage in a cell therapy approach. Therefore, identifying the key mechanisms of gut microbiota and their products in regulation of macrophage phenotypes in the intestine needs further investigation for the development of an effective therapeutic approach for treating gut leakage and its associated diseases.

8. Current treatment strategies

Growing evidences show a clear association of gut leakage with several diseases at extraintestinal distinct organs including liver, lung, brain, and metabolic diseases like obesity, etc. Leaky gut syndrome is a theory that intestinal permeability is not only a symptom of gastrointestinal disease, but also an underlying cause that develops independently. Currently, the suggested treatment options are probiotics to restore gut barrier function. This treatment may help maintain the health of gut lining by preventing overgrowth of pathogenic bacteria in the gut. However, the ability of probiotics to recover intestinal barrier function needs further investigation. The other treatment option is prebiotics, usually plant fibers that might feed beneficial gut bacteria. For, example, avoiding dietary fats and sugars, which diminish pathobionts, could support the growth of beneficial gut bacteria. Moreover, a diet format, the low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols [short-chain carbohydrates (sugars) that the small intestine absorbs poorly]) diet has been suggested for the treatment of irritable bowel syndrome and/or small intestinal bacterial overgrowth. FODMAP foods are assumed to aggravate the gut leakage; however, there are no scientific evidences available. In addition, bacteria such as aerotolerant lactobacilli or wound-associated *Akkermansia muciniphila* might be critical for wound and anastomotic healing in the gut.[135] Moreover, kinase inhibiting drugs like ruxolitinib were found to alleviate inflammation, apoptosis, and intestinal barrier leakage in UC via STAT3.[136] Vitamin D and the amino acid L-glutamine may specifically help repair gut lining[137,138]; however, more evidence is required to conclude these experimental findings. Nevertheless, there are certain limitations in treatment with probiotics and dietary habits. For example, designed dietary habits are considered difficult to follow with a modern lifestyle and the probiotics might induce unfavorable gut dysbiosis and further exaggerate the conditions. Fecal microbiota transplantation (FMT) has shown promising effects in experimental studies,[139] while a single clinical study using total gastrointestinal flora transplantation showed a success rate of 89.3% in attenuating leaky gut syndrome.[140] However, the persistence of favorable microbiota after FMT in the long term is still debatable, and further studies are required. Therefore, there is an urgent need to search for new therapeutic options to treat gut leakage that stands as an underlying condition for several other diseases.

9. Future perspectives

In the decades after their discovery, macrophages have been suggested as promising targets in almost all areas of biomedical research. Developments in the field of macrophage research in the past decade have led to a better understanding of the maturation and differentiation dynamics of this cell type. Accumulating evidence suggests that, apart from their well-known role in phagocytosis and foreign-antigen recognition, macrophages are endowed with high functional plasticity allowing them to acquire pro- or anti-inflammatory and tissue-reparative phenotypes during the course of inflammation, dependent on the signals that they receive from the surrounding cells or from the pathogen itself. Given that the injury specific signals derived from the local microenvironment are integrated to generate specific macrophage polarization patterns, we hypothesize that different compositions of microbiota dysbiosis generate unique macrophage polarization patterns at defined time points during inflammation or infection, to serve the needs of the infected/inflamed intestinal niche. A better understanding of these processes would allow the selective targeting of the macrophage pool for better host defenses and accelerated intestinal epithelial barrier repair. Despite there being studies showing a relation between microbiota and macrophage phenotype, their released specific mediators that are involved in tissue repair are not well studied. Probiotics and FMT have been investigated in clinical trials for the treatment of gut leakage–associated diseases including type 1 diabetes, multiple sclerosis, and rheumatoid arthritis.[141] Therefore, there is an urgent need to conduct experimental studies that focus more on those specific macrophage subsets with distinct functions and their relation to different compositions of microbiota to investigate their specific targets and released mediators, which would help explain those events instrumental in mediating pro- and anti-inflammatory mechanisms. This would help us to understand the microbiota induced macrophage-derived mediators and their interactions in an inflammatory microenvironment. Understanding these mechanisms would enable innovative therapeutic approaches like in situ repolarization toward a regulatory or tissue-reparative phenotype and ex vivo generation of regulatory macrophages as a cell-based therapy to target host defense, termination of inflammation, and tissue repair, to reduce intestinal epithelial barrier damage.

In addition, other possibilities of modulating microbiota and their metabolites, and so in turn the functional phenotype of the intestinal macrophages, must be considered. In one study, microbes like *Lacticaseibacillus casei* strain Shirota were shown to modulate intestinal epithelial cell barrier integrity in vitro via macrophages through their bacterial sensing ability and cytokine

production.[142] Interestingly, the microbial metabolite butyrate was observed to be a potential regulator of epithelial barrier integrity in both in vivo and in vitro studies, by driving macrophages to an M2 phenotype determined by the expression of CD206 and arginase-1, Fizz1, and Ym1, and was proposed as a candidate therapeutic target for UC.[130,131] However, in the future, the evidence for employing microbiota-derived metabolites to target macrophage plasticity, regulating the release of prorepair mediators including extracellular vesicles, to generate the reprogrammed/re-engineered macrophages and association of prorepair macrophages and microbiota must be explored in detail.

Furthermore, the underlying pathological mechanisms of gut leakage–associated diseases remain mostly unknown. Moreover, the precise part of the intestine (proximal or distal) where epithelial barrier dysfunction initially occurs has yet to be determined. Furthermore, there need to be established gut leakage animal models to enable further investigations and proof of concept for developing promising therapies. Finally, the role of nonbacterial microbiota like the virome, mycobiome, etc. must also be carefully considered in future investigations.

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Author contributions

B.S. and R.S. planned and structured the manuscript. B.S. drafted the first draft and generated tables and figures. P.S. wrote a section and revised the manuscript. R.S. critically reviewed and submitted the manuscript. All authors contributed to manuscript revision and approved the submitted version.

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