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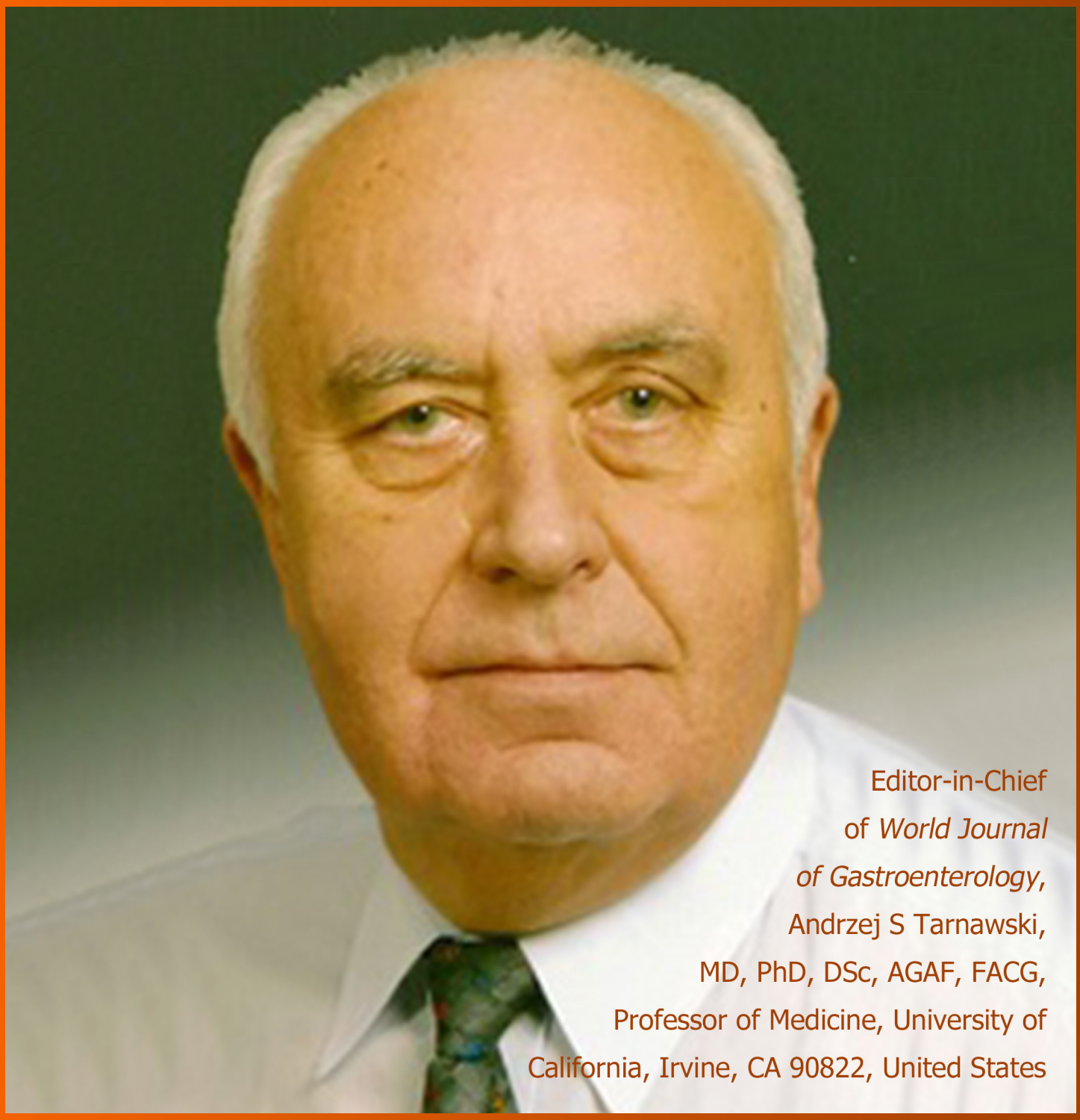

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REVIEW

Crohn's disease as the intestinal manifestation of pan-lymphatic dysfunction: An exploratory proposal based on basic and clinical data

Yu-Wei Zhou, Yue Ren, Miao-Miao Lu, Ling-Ling Xu, Wei-Xin Cheng, Meng-Meng Zhang, Lin-Ping Ding, Dong Chen, Jian-Guo Gao, Juan Du, Ci-Liang Jin, Chun-Xiao Chen, Yun-Fei Li, Tao Cheng, Peng-Lei Jiang, Yi-Da Yang, Peng-Xu Qian, Peng-Fei Xu, Xi Jin

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Abstract

Crohn's disease (CD) is caused by immune, environmental, and genetic factors. It can involve the entire gastrointestinal tract, and although its prevalence is rapidly increasing its etiology remains unclear. Emerging biological and small-molecule drugs have advanced the treatment of CD; however, a considerable proportion of patients are non-responsive to all known drugs. To achieve a breakthrough in this field, innovations that could guide the further development of effective therapies are of utmost urgency. In this review, we first propose the innovative concept of pan-lymphatic dysfunction for the general distribution of lymphatic dysfunction in various diseases, and suggest that CD is the intestinal manifestation of pan-lymphatic dysfunction based on basic and clinical preliminary data. The supporting evidence is fully summarized, including the existence of lymphatic system dysfunction, recognition of the inside-out model, disorders of immune cells, changes in cell plasticity, partial overlap of the underlying mechanisms, and common gut-derived fatty and bile acid metabolism. Another benefit of this novel concept is that it proposes adopting the zebrafish model for studying intestinal diseases, especially CD, as this model is good at presenting and mimicking lymphatic dysfunction. More importantly, the ensuing focus on improving lymphatic function may lead to novel and promising therapeutic strategies for CD.

Key Words: Inflammatory bowel disease; Crohn's disease; Lymphatic system; Inside-out model; Immune cells; Zebrafish

Core Tip: The lymphatic system plays an active role in the pathogenesis, progression, and complications of certain diseases. Our review proposes an innovative concept of pan-lymphatic dysfunction and suggests Crohn's disease (CD) as the intestinal manifestation of pan-lymphatic dysfunction using basic and clinical preliminary data, which may bring new perspectives to both the scientific study and clinical management of CD.

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INTRODUCTION

The lymphatic system in humans consists of lymphatic vessels and lymphoid tissues and organs, allowing the unidirectional transport of fluid, cells, and molecules[1], and thereby playing a functional role in fluid homeostasis, immune cell trafficking, and lipid absorption[2,3]. Lymphatic system dysfunction has been demonstrated in various conditions including obesity, cardiovascular disease, chronic inflammation, atherosclerosis, neurological disorders, hypertension, and elephantiasis[4,5]. Recently emerging novel technologies, such as single-cell analysis and intravital imaging, have revealed novel characteristics of lymphatic dysfunction in various diseases and the extensive heterogeneity of lymphatic vessels[6]. Moreover, interventions targeting the lymphatic system have yielded ground-breaking results. Nevertheless, the prevalence and impact of disease-associated lymphatic dysfunction remain underestimated. Therefore, we propose an innovative concept of disease-associated pan-lymphatic dysfunction as an updated theory using the gut, which acts as a reservoir of bacteria and immune cells and has a lymphatic system which plays a predominant role in inflammation and immune regulation, as an example[4,7,8]. Among the various gut-associated diseases, the importance of the lymphatic system in Crohn's disease (CD) has received increasing attention, but has not yet been systematically summarized. Here, we review the molecular, cellular, and clinical evidence for lymphatic dysfunction in CD and propose that CD is the intestinal manifestation of pan-lymphatic dysfunction. The benefits of this concept for animal model development and clinical management are also discussed.

RATIONALE FOR CONSIDERING CD AS THE INTESTINAL MANIFESTATION OF PAN-LYMPHATIC DYSFUNCTION

CD is a form of inflammatory bowel disease (IBD) characterized by transmural damage and skip lesions. It can involve the entire gastrointestinal (GI) tract but the most common affected segments are the terminal ileum and the colon[9]. Although the mechanism underlying the development of CD remains unknown, a dysregulated immune system, altered microbiota, genetic susceptibility, and environmental factors are major contributors to its onset and progression[10]. The long-term therapeutic effects of commonly used drugs are unsatisfactory, and approximately 80% of patients require

surgery 20 years after disease onset[11]. Furthermore, these drugs are associated with various adverse effects and uncontrolled immunogenicity[2,4]. Because mucosal healing is the optimal therapeutic outcome[10], it is crucial to understand the pathogenesis and processes of mucosal pathological alterations in CD. We provide evidence to suggest that CD is the intestinal manifestation of pan-lymphatic dysfunction (Figure 1), which may lead to the development of novel therapeutic strategies and the optimization of CD management.

Pathological changes of the lymphatic system supporting its fundamental involvement in CD

The gut lymphatic system is composed of lymphatic vessels, mesenteric lymphatic nodes (MLNs), and gut-associated lymphatic tissues, including Peyer's patches (PPs) and isolated lymphoid follicles. Lacteals (also called lymphatic capillaries) and submucosal and mesenteric lymphatic vessels represent the three structural levels of the intestinal lymphatic vasculature[12]. Loss or dysfunction of the intestinal lymphatics causes severe gut inflammation, infection, and sepsis, with 100% lethality by 60 h in a mouse model[12,13]. Several functional and morphological alterations in the lymphatic system are well-recognized features of CD, including lymphangiogenesis, lymphadenopathy, and lymphatic vessel dysfunction[5,14]. Patients with CD have a higher density of lymphatic vessels than controls[15]. However, their functional fluid drainage and anti-inflammatory capacities are impaired[16], demonstrating the lymphatic phenomenon of "increased quantity but decreased quality" in CD. Lymphatic vessel dysfunction, including lymphangiectasia and lymphangitis, leads to lymphatic hyperpermeability, interstitial edema, lymphostasis, granulomatous inflammatory response, and lymphatic vasculature obstruction[17,18]. Button junctions, which are closely associated with lymphatic capillary permeability and intestinal material exchange, are lost during inflammation[12]. The submucosal and mesenteric collecting lymphatic vessels are also damaged during intestinal inflammation, as shown by increased junction permeability, flawed valves, and decreased smooth muscle pumping activity[12,19].

Previous studies have revealed several intriguing phenomena suggesting a lymphatic basis of CD. Initial lesions in CD occur in the lymphoid follicles and PPs in the colon and ileum, respectively[20]. Moreover, intestinal lymphatics are intimately associated with the gross segmental distribution of intestinal lesions, with longer CD segments in the ileum consistent with longer lymphatic collecting ducts[14]. The microscopic characteristics of CD further support the active involvement of lymphatics, as granulomas appear in and around lymphatic vessels[21]. Furthermore, several studies have indicated that granulomas in the MLNs of patients with CD may cause lymphatic obstruction[21] and increase the risk of recurrence after ileocolonic resection[22]. From a clinical standpoint, previous studies have indicated that decreased lymphatic vessel density is associated with disease and the postoperative endoscopic recurrence of CD[23].

Inside-out model of CD pathogenesis reveals the long-ignored pathological effect of the lymphatic system in CD

Currently, there are two opposing models of CD pathogenesis: outside-in and inside-out[24]. The conventional outside-in model regards luminal bacteria-induced mucosal damage as the initial event in CD and submucosal injury as the ensuing terminal event. However, some evidence contradicts this theory of a primary mucosal injury. A study on nucleotide-binding oligomerization domain-2 $(NOD2)^{-/-}$ mice revealed that macrophages, rather than epithelial cells, are the predominant abnormal cell type during gut inflammation[25]. Therefore, the long-overlooked inside-out model, in which infection or inflammation by intracellular bacteria and their metabolites in the intestinal lymphatic system is the initial event in CD, leading to mucosal inflammation, may be better supported by the evidence. This model, which emphasizes the significance of the lymphatic system, supports our hypothesis of CD as a pan-lymphatic dysfunction and can be divided into three phases (Figure 2).

Phase I: Infection by intracellular bacteria: The inside-out model proposes that infection by intracellular bacteria and their metabolites occurs as the first stage of CD pathogenesis without obvious mucosal pathology. The importance of gut bacteria in CD was shown by a previous study in which ileitis and colitis did not occur in the absence of bacterial flora [14]. Genetic studies have revealed several specific genes associated with CD, including NOD2, ATG16L1, and IRGM[26]. The proteins encoded by these genes are involved in intracellular pathogen elimination *via* autophagy, indicating that this process is impaired in CD. Several studies have shown that MLN dysbiosis in CD is characterized by an overabundance of Proteobacteria, such as *Escherichia*, *Shigella*, *Helicobacter*, and *Salmonella*[20,27]. Intriguingly, *Salmonella* can invade PPs and MLNs with few signs of intestinal mucosa injury[28]. Adherent invasive *Escherichia coli* strains isolated from CD patients can survive within macrophages without inducing cell death[29]. These findings suggest that intestinal bacteria can invade the mucosa without resultant inflammation. Importantly, a study on postoperative recurrence in patients with CD showed significant inflammatory cell infiltration of the lamina propria, whereas only small intestinalulcers were detected in the ileal mucosa[24]. Based on this evidence, we suspect that bacterial invasion of the lymphatic system occurs prior to the development of mucosal lesions.

Phase II: Pathogens infect and persist in intestinal lymphatic tissues: The inside-out model states that pathogen invasion of MLNs through lymphatic vessels causing persistent infection is critical for CD progression. Pathological bacterial translocation (PBT) to MLNs is well established in CD[20]; detection of bacterial DNA in MLNs using high-throughput sequencing indicates that PBT is a non-selective process[30]. A study on acute intestinal infection by *Yersinia pseudotuberculosis* revealed that an 'immunological scar' persists in the gut lymphatics even after pathogen eradication [31]. Remodeling of the lymphatic system and a deviation of the immune response disrupts communication between the tissue and the immune system, compromising homeostasis. Notably, there are many similarities between *Y. pseudotuberculosis* infection and CD. Lymphangitis and lymphatic vascular dysfunction are also common in CD. More importantly, PBT to MLNs[20,32] and mesenteric adipose tissue[20,33] as well as defects in dendritic cell (DC) migration[33,34] have been described in CD. Moreover, CD-induced lymphadenopathy remains after the resolution of acute intestinal inflammation in a dextran sodium sulfate (DSS) model of colitis[35]. Therefore, we speculate that such an 'immunological scar'

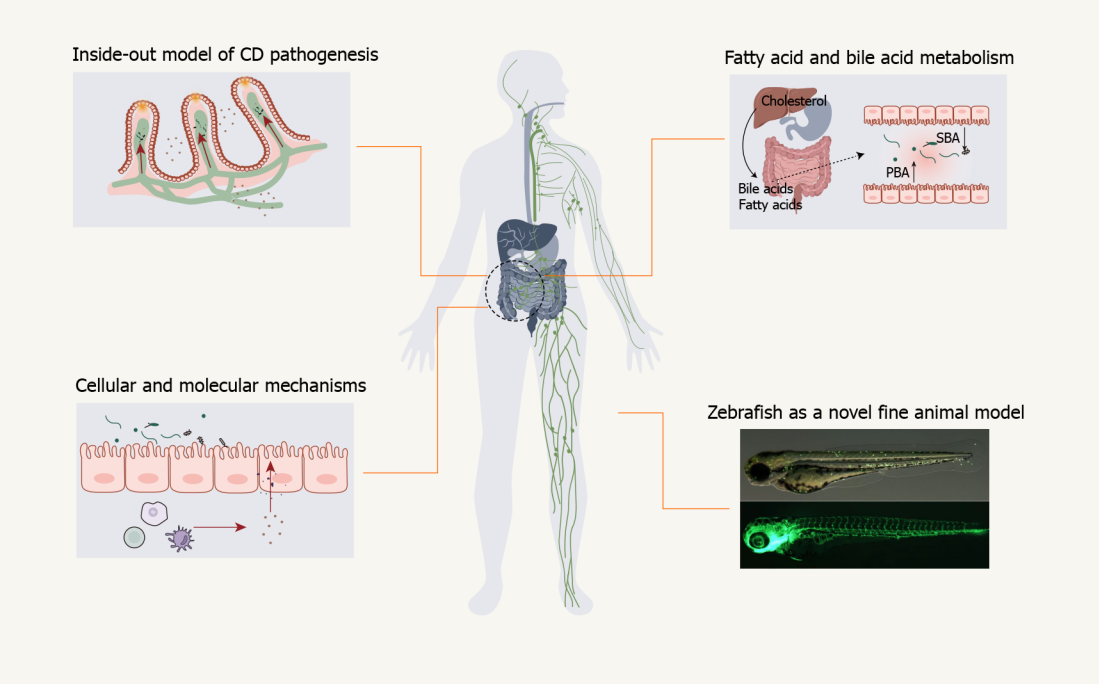

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Figure 1 Flowchart for Crohn's disease as the intestinal manifestation of pan-lymphatic dysfunction. The following factors are considered: inside-out model, fatty acid/bile acid metabolism, cellular/molecular mechanisms, and zebrafish as a novel fine animal model. CD: Crohn's disease; PBA: Primary bile acid; SBA: Second bile acid.

Inside-out model of CD pathogenesis

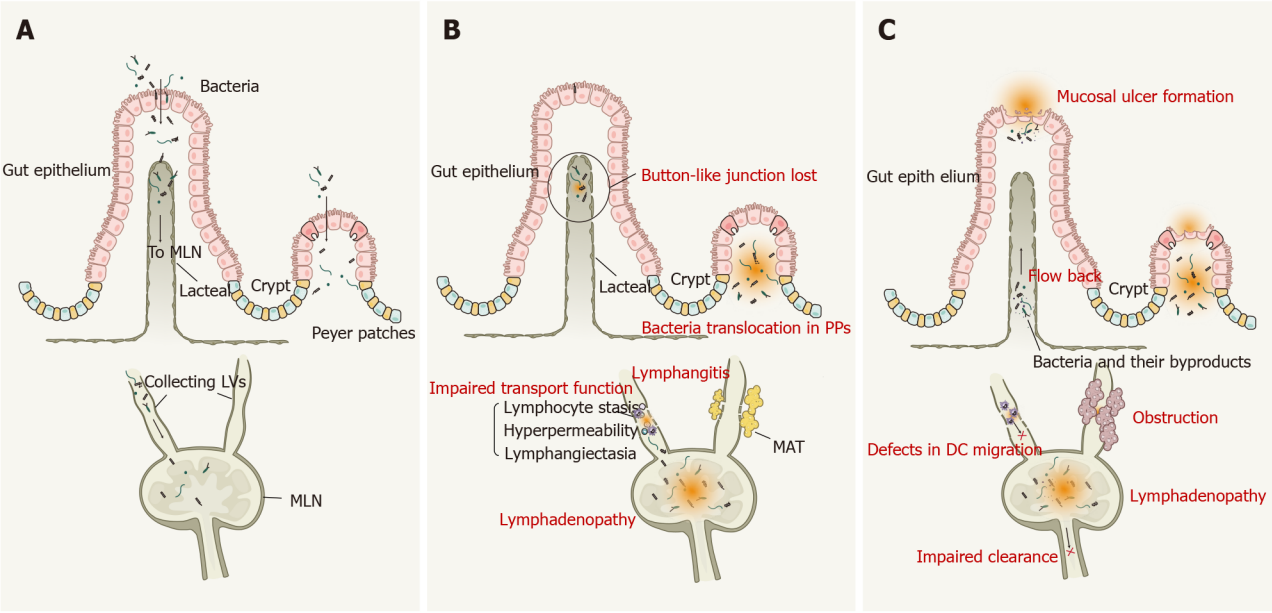

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Figure 2 Inside-out model of Crohn's disease pathogenesis. A: Phase I, intracellular bacteria infect into lymphatic system with few signs of intestinal mucosal injury; B: Phase II, Pathogens infect and persist in intestinal lymphatic tissues, which causes an 'immunological scar' in the intestinal lymphatic system. The impaired transport function, lymphangitis, lymphadenopathy, loss of button-like junctions, bacteria translocation to mesenteric lymph nodes and Peyer's patches, and mesenteric adipose tissue formation have been found in the pathogenesis of Crohn's disease (CD); C: Phase III, Mucosal injury as the terminal event of CD. Lymphatic dysfunction, including impaired clearance, defective dendritic cells migration, and obstruction, provides opportunities for bacteria and their by-products flowing back to the draining lymphatic vessels and causing mucosal lesions. DC: Dendritic cells; MLN: Mesenteric lymph nodes; PPs: Peyer's patches.

also exists in CD, which alters GI immunity and the lymphatic system, ultimately leading to persistent intestinal lesions.

Phase III: Mucosal injury as the terminal event of CD: Mucosal injury is considered the terminal event in the inside-out model. A breakthrough study used formalin injections to block certain segments of the mesenteric lymphatics of the small intestine, establishing experimental enteritis resembling CD[24]. This indicates that intestinal lymphatic blockage or malfunction are essential for the initiation of mucosal injuries. Bacteria and their by-products are retained in the MLNs. During intestinal inflammation, mesenteric collecting vessel function is impaired owing to increased junction permeability, defective valves, and reduced smooth muscle cell pumping activity[19]. This lymphatic dysfunction provides opportunities for bacteria and their by-products to flow back into the draining lymphatic vessels, aggravating intestinal inflammation and causing mucosal lesions. Moreover, the compromised integrity and hyperpermeability of lymphatic vessels prevent the routine drainage of antigens and immune cells into the MLN. In SAMP1/YitFc mice, inhibiting DC trafficking to lymph nodes induced ileitis resembling CD[36].

Interactions between immune cells and the lymphatic system and the immune dysfunction caused by CD further support the importance of the lymphatic system

The gut lymphatic system and the immune cells within it not only play a critical role in the pathogenesis of CD[37] but are also influenced by the immune dysfunction induced in CD, revealing a two-way interaction. In addition, immune and non-immune cells have been shown to exhibit increased plasticity in CD to compensate for lymphatic dysfunction, with enhanced lymphatic system contact, lymphatic phenotype changes, and expression of lymphocyte surface markers. A partial overlap between the molecular mechanisms involved in lymphatic function and CD was also identified; this complex network is summarized at both the cellular and molecular levels in Figure 3.

Immune cell disorders and changes of cell plasticity further support the importance of the lymphatic system in CD: Lymphatic dysfunction contributes to CD pathogenesis by altering the influx of immune cells. Importantly, CD initiation is tightly correlated with B and T cell trafficking between the bloodstream, intestinal mucosa, and lymphatic system[38,39]. An increasing number of studies have suggested that the unique cytokine milieu produced by immune cells in MLNs leads to a dysregulated T helper (Th)1/Th17 immune response in CD[7,38,40]. Th1 cells mainly secrete tumor necrosis factor (TNF)-α and interferon (IFN)-γ while Th17 cells primarily produce interleukin (IL)-17, IL-22, and TNF-α[41]. Th1 polarization has been detected in the PPs of patients with active CD[42] and an increase in specific pro-inflammatory DC subsets has been observed in the MLNs of both animal models of colitis and patients with CD[43,44]. Moreover, long-lasting 'immunological scars' promote DC migration and increase susceptibility to further infections[35]. The impairment of DC migration due to lymphatic dysfunction and dysregulated chemokines in CD leads to mature DCs moving away from their usual MLNs and causes the proliferation of T cells, contributing to the formation of tertiary lymphoid tissue [34,45]. Macrophages are involved in both acute inflammation and inflammation-associated lymphangiogenesis[46]. $CD169^+$ macrophages differ from M1 and M2 macrophages and are located in MLNs, where they produce high levels of pro-inflammatory cytokines and may participate in Th17 responses[7]. Type 3 innate lymphoid cells (ILCs), the inappropriate activation of which causes IL-17 and IL-22 overproduction, are responsible for CD pathogenesis and progression [47]. Importantly, ILC3 also play a critical role in the generation of lymphoid structures[48], further supporting the role of the lymphatic system in CD.

Disordered immune cells are directly associated with alterations in the lymphatic vasculature. The observed increase in tissue macrophages, T cells, and neutrophils in CD reflects the failure of the direct clearance of inflammatory cells due to impaired lymphatic function[49]. Structural (dilated torturous lymphatic vessels) and functional (greater submucosal edema, higher immune cell burden) changes were associated with elevated colonic neutrophil, macrophage, and T cell infiltration in a mouse model of experimental colitis[50]. DCs, monocytes, mast cells, macrophages, T cells, and B cells are actively involved in the induction of lymphangiogenesis during inflammation by mediating the expression of lymphangiogenic factors[50]. B cells and ILCs have been observed in the inflamed bowel walls of patients with CD and may contribute to lymphatic remodeling[34]. Impaired lymphatic transport exacerbates the accumulation of inflammatory cells[49], forming a vicious cycle of lymphatic dysfunction in CD.

Several cell types show enhanced cell plasticity with altered characteristics and functions when exposed to an inflammatory milieu. For instance, lymphocytes from MLNs display Th1 and Th17 characteristics in CD, while regulatory T cell (Treg)-Th17 and Th17-Th1 trans-differentiation has also been observed[51]. In addition, an imbalance between ILC3 and ILC1 was detected in the gut mucosa of patients with CD, and the possibility of ILC3 deviating towards ILC1 was identified[47]. Interestingly, monocytes can present lymphatic phenotypes and express lymphatic endothelial markers such as lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1), prospero homeobox protein 1 (Prox-1), and podoplanin in certain inflammatory environments[52]. Finally, macrophages play a critical role in promoting lymphangiogenesis in response to lymphatic dysfunction caused by inflammation[46]; lymphangiogenic macrophages may differentiate into lymphatic endothelial cells (LECs) and be directly incorporated into lymphatic vessels[50].

Cells other than immune cells also interact with the lymphatic system and play pathological roles in CD. Platelet aggregation in lymphatic vessels may prevent blood flow. Increased platelet levels are often observed in patients with severe CD[53], suggesting that aggregation of platelets in these patients may decrease the unidirectional flow of lymph fluid. Moreover, platelets can interact with podoplanin and inhibit the proliferation of LECs, suppressing the formation of lymphatic vessels and lymphatic-venous connections[54,55]. Intestinal stem cells (ISCs) maintain the epithelium by replacing cells through self-differentiation[12]. A previous study showed that depletion of ISC niche factors alters epithelial differentiation in a mouse model of CD-like ileitis[56]. Interestingly, crypt lymphatics act as an important source of niche factors for ISC[57], consistent with the critical role of LECs in ISC homeostasis and injury-mediated

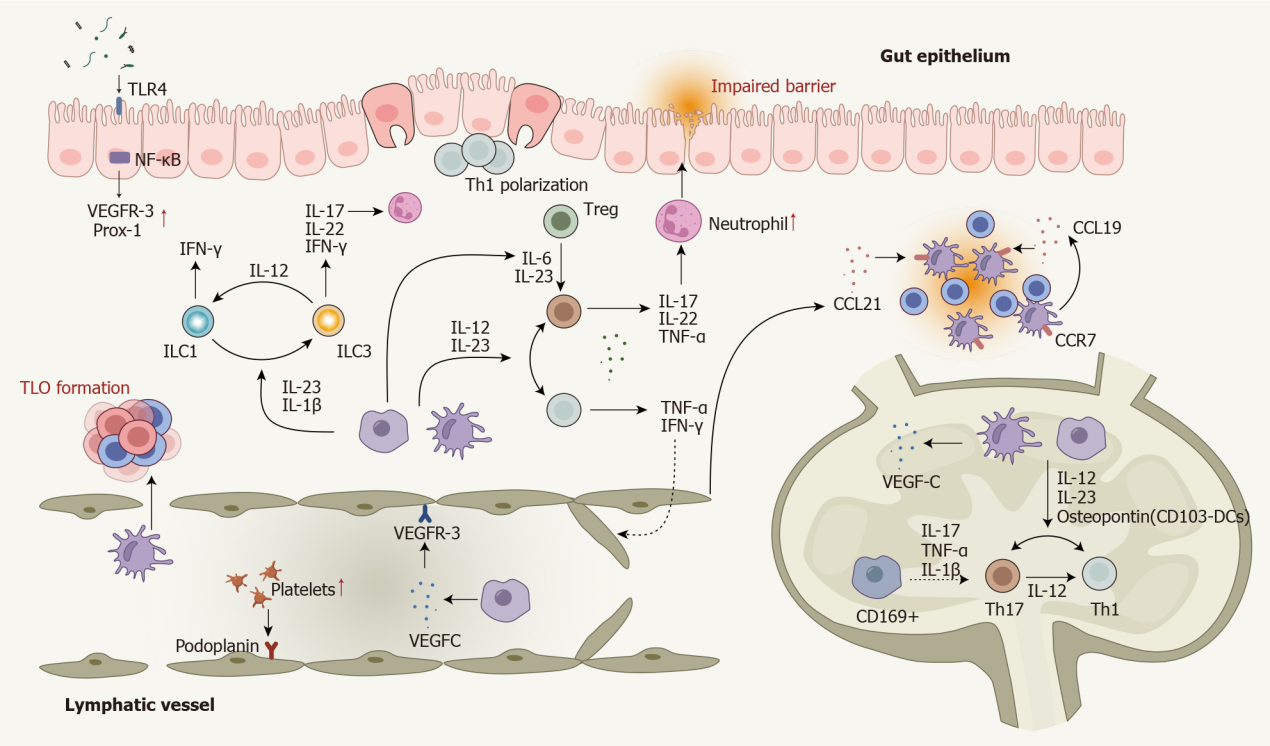

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Figure 3 Dysregulated cells, cytokines, and enhanced cell plasticity in the lymphatic system in Crohn's disease. T cells are polarized to Th1 and Th17 cells in response to pro-inflammatory cytokines produced by macrophages and dendritic cells (DCs). Several cytokines play roles in Th17-Th1 and Treg-Th17 trans-differentiation. DCs, macrophages, T cells, and B cells contribute to lymphangiogenesis by mediating the expression of lymphangiogenic factors. Impaired lymphatic function and dysregulated chemokines lead mature DCs and T cells away from their usual mesenteric lymph nodes. Innate lymphoid cells (ILCs) also contribute to Crohn's disease (CD) pathogenesis and enhanced plasticity between ILC1 and ILC3 has been observed. Several signaling pathways involved in the lymphatic system actively participate in the CD pathogenesis. Nuclear factor-kappa B is involved in lymphatic remodeling by directly up-regulating the expression of VEGFR-3 and Prox-1. The mTOR signaling affects leukocyte trafficking through the lymphatic barrier in CD. CD: Crohn's disease; DC: Dendritic cells; IFN: Interferon; IL: Interleukin; ILC: Innate lymphoid cell; NF-κB: Nuclear factor-kappa B; Prox-1: Prospero homeobox protein 1; Th: T helper; TLO: Tertiary lymphoid organ; TLR4: Toll-like receptor 4; TNF: Tumor necrosis factor; Treg: Regulatory T cell; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; MAT: Mesenteric adipose tissue.

regeneration[58]. Therefore, lymphatic dysfunction and obstruction can directly influence ISCs, leading to epithelial barrier impairment.

Partial overlap of lymphatic system and CD molecular mechanisms reinforces crosstalk: Several regulatory pathways in the intestinal lymphatic system are involved in the pathogenesis of CD. For instance, vascular endothelial growth factor (VEGF)-C-VEGF receptor (VEGFR)3 signaling is critical to maintain intestinal lymphatic function during inflammation. VEGFR3 inhibition aggravates colitis symptoms in animal models[59]. In contrast, VEGF-C has a protective function in experimental colitis, causing increased inflammatory cell mobilization and bacterial antigen clearance from the inflamed site to the draining lymph nodes by signal transducer and activator of transcription 6-dependent macrophages[60]. The lacteals play significant roles in dietary fat absorption and the gut immune response[50], and are continuously regenerated through cell proliferation mediated by signaling *via* Notch and its ligand delta-like-4 (DLL4)[12,61]. Notably, the expression levels of Notch signaling-related genes and DLL4 were decreased in SAMP1 mice that spontaneously develop CD-like ileitis[56]. The VEGFR3-phosphoinositide 3-kinase (PI3K) signaling pathway is another important regulatory axis in lymphatic vasculature development, and activation of the PI3K-AKT-mammalian target of rapamycin (mTOR) pathway is involved in CD pathogenesis[62]. The mTOR signaling pathway plays a pivotal role in CD[63] and a recent study revealed its active involvement in intestinal lymphatic function through effects on leukocyte trafficking in patients with CD[64]. Additionally, angiopoietin-TIE signaling contributes to whole-body lymphatic vessel development and is important for mesenteric lymphatic development and maintenance[65,66]. Intriguingly, dysregulated angiopoietin levels have been observed in patients with CD[67] and the targeting of this pathway with thalidomide represents a potential treatment strategy[68].

Toll-like receptor 4 (TLR4) is an important component of inflammatory signaling pathways in the GI tract[69]. A previous study suggested that TLR4 expressed on enterocytes plays an important role in phagocytosis and bacterial translocation across the intestinal barrier[70]. TLR4 activation also mediates mesenteric lymphatic alterations in a DSS mouse model of colitis[71]. The major downstream component of the TLR4 signaling pathway, nuclear factor-kappa B (NF-κB), also plays a significant role in inflammation regulation, and its inappropriate activation has been described in CD[72]. Furthermore, NF-κB contributes to lymphatic remodeling by directly up-regulating VEGFR3 and Prox-1 expression[73]. Sphingosine-1-phosphate (S1P) is a pleiotropic lipid mediator that plays a significant role in inflammation

by regulating lymphocyte trafficking[74]. The reduction of lymphocyte gut homing by S1P receptor agonists has shown profound therapeutic effects in both colitis models and patients with CD[75-77].

Inflammatory cytokines produced by various cells play central roles in intestinal inflammation caused by CD and contribute to lymphatic structure dysregulation. IL-17 recruits neutrophils, thereby enhancing intestinal permeability [47]. TNF is a significant factor in CD and its close relationship with the lymphatic system has been demonstrated. TNF can also disrupt lymph flow and immune cell migration through impaired lymphatic valves and ileitis-associated tertiary lymphoid organs[78]. The NOD2 mutation associated with CD affects IL-1β expression and processing. IL-1β stimulates lymphatic proliferation but down-regulates angiopoietin 1 expression[15], contributing to the impaired integrity of, and leakage from, lymphatic vessels. Also, IL-1β and IL-23 participate in ILC3-ILC1 plasticity[47]. IL-3 is another critical regulator of lymphatic development that controls LYVE-1 and podoplanin expression. Notably, a reduction in monocyte-derived IL-3 in the lamina propria has been observed in patients with CD[79]. IL-6, produced by monocytes, macrophages, and endothelial cells, is pivotal for intestinal inflammation in CD, as it controls the balance between pro-inflammatory T cells and Tregs[80]. The presence of IL-6 and/or IL-23 can stimulate the differentiation of Tregs into Th17 cells[41]. Prox1 is a lymphatic-specific transcription factor, and Prox1 knockout mice do not develop any lymphatic vascular structures and experience increased lymph leakage[81]. Decreased Prox1 Levels are associated with the postoperative recurrence of CD[82]. Higher levels of CCL21 and CCL19 have been detected at the site of inflammation in patients with CD; these chemokines recruit mature DCs and proliferating T cells through their ligand, CCR7[45]. The chemokine decoy receptor D6 can limit inflammation by scavenging inflammatory chemokines; a significant increase in the levels of this receptor has been reported in the lymphatic vessels of patients with CD[8]. $D6^{-/-}$ mice have higher levels of pro-inflammatory chemokines than controls, and are more susceptible to experimental colitis[83]. Glucagon-like peptide 1 (GLP-1) is the classic incretin involved in glucose regulation, and its postprandial levels are higher in the gut lymph than in the blood[84]. Abnormal postprandial GLP-1 secretion has been observed in patients with CD[85].

Gut-derived fatty and bile acid metabolism mediate lymphatic dysfunction in CD

The pathogenesis of CD is closely related to dysbiosis of the intestinal microbiota. Metabolomic analysis revealed that the intestinal microbiota imbalance is characterized by changes in bile and fatty acid metabolism[86]. Recently, bile and fatty acid dysregulation has been emphasized in CD because they are closely related to intestinal homeostasis and inflammation[87,88]. Moreover, their association with the lymphatic system has been suggested.

Lymphatic vessels play a significant role in lipid absorption[5] and provide the main cholesterol drainage route from the interstitium[89]. A previous study showed that cholesterol synthesis and absorption is altered by the low serum levels of total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein (HDL) cholesterol detected in active CD[90], reflecting the impaired drainage of lymphatic vessels. HDL cholesterol exerts anti-inflammatory effects in CD models[91] and affects LECs in the presence of pro-inflammatory cytokines[5]. Importantly, abnormal lymphatic drainage can lead to chylomicron leakage and fat accumulation around the mesenteric tissues[34], forming creeping fat, a recently recognized feature of CD. Creeping fat plays a significant role in intestinal fibrosis and stricture formation in CD[92]. It is also a vital target site for PBT in CD[20], serving as a reservoir for pathological bacteria that results in persistent inflammation. MAT hypertrophy in patients with CD also influences lymphoid dysfunction through the activated NF-κB signaling pathway[93]. Additionally, the aberrant interaction of perinodal adipose tissue (PAT) and the lymphatic system might contribute to CD by reducing the polyunsaturated fatty acid supply from PAT to MLNs[94]. Intriguingly, adipocytes surrounding draining lymph nodes perform immunological functions after subcutaneous bacterial infection [95].

Bile acids (BAs) are primarily reabsorbed in the terminal ileum and colon, and malabsorption of BAs is a well-established characteristic of patients with CD. Further metabolomic studies have shown impaired BA metabolism in patients with CD, with an increase in primary BAs (PBAs) and a reduction in secondary BAs (SBAs). Moreover, interactions between BAs and various immune cells, including ILC3, Th17 cells, DCs, monocytes, and macrophages, have been reported[87]. For example, SBAs and their derivatives can inhibit Th17 differentiation and promote macrophage and DC differentiation[87,96], which ultimately suppresses gut immune responses. Intriguingly, previous studies have demonstrated that bile flow obstruction leads to mucosal injury with intestinal hyperpermeability and bacterial overgrowth, and increased bacterial translocation to MLNs[97]. However, the role of the lymphatic system in BA-related CD pathogenesis requires further investigation.

RECOGNIZING THE IMPORTANCE OF THE LYMPHATIC SYSTEM IN CD USING ZEBRAFISH AS A RESEARCH MODEL

Owing to their rapid development, transparent embryos and larvae, small size, and strong reproductive ability, zebrafish have become a popular model for studying embryonic development and human disease. Importantly, zebrafish are similar to mammals, not only in embryonic development, gene regulation networks, and organ morphology and physiology, but also in the pathological processes of many human diseases. Moreover, high-throughput genetic and drug screening can be easily performed in zebrafish[98]. In addition, the cellular composition and architectural organization of the intestinal tract are highly conserved between zebrafish and mammals. Similar to mammals, the enteric nervous system (ENS) of zebrafish is derived from neural crest cells and is comparable to mouse and human ENS based on gene expression and functional studies[99]. Therefore, zebrafish are ideal for studying human intestinal diseases (Figure 4).

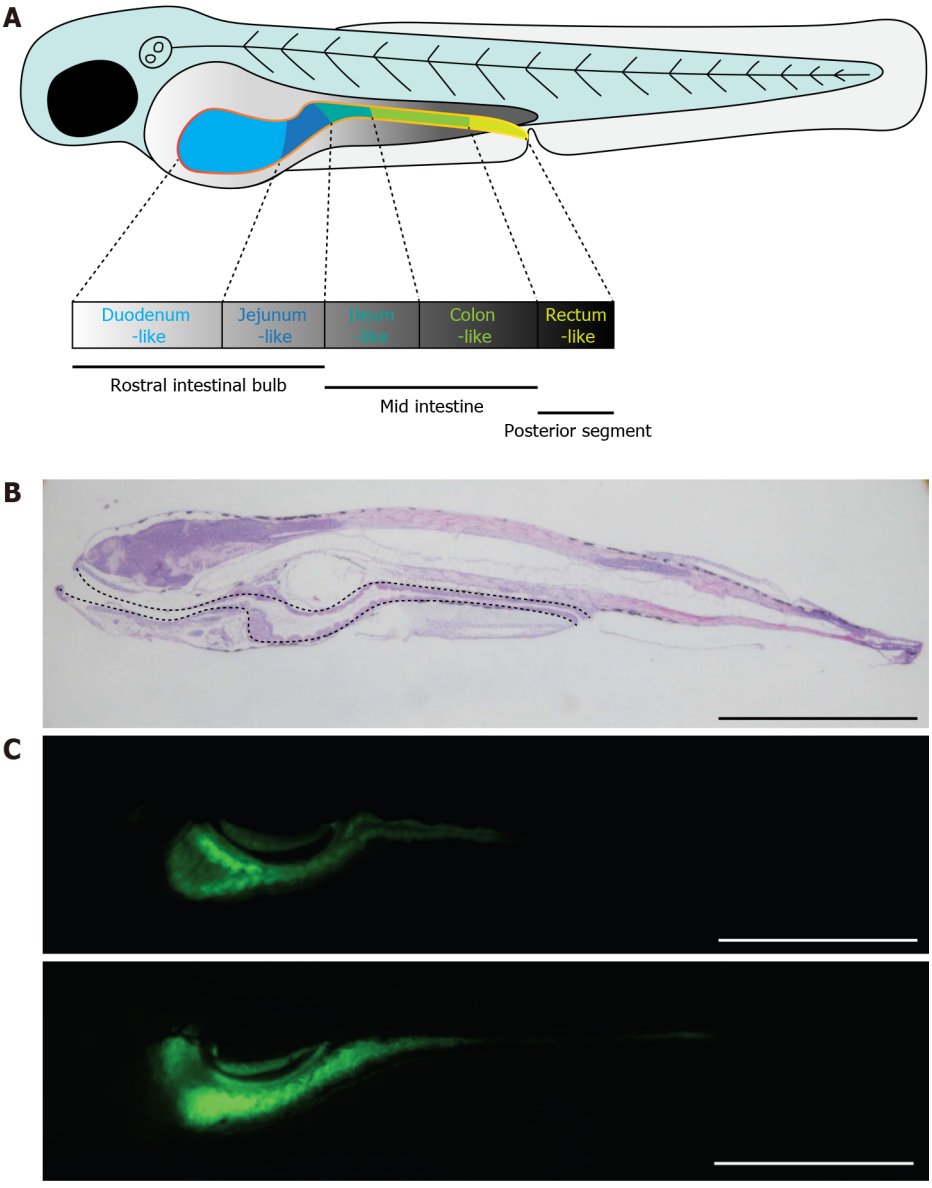

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Figure 4 Zebrafish as a good candidate model for the study of Crohn's disease. A: Schematic diagram showing the morphology of zebrafish embryo at 5 dpf. The solid yellow line indicates the intestine of the embryo; B: Morphology of zebrafish embryo visualized by hematoxylin and eosin staining of embryonic sections at 5 dpf. Sections were cut along the sagittal plane. The dotted line indicates the whole intestine; C: Fluorescence signals of ET33J1: enhanced green fluorescent protein zebrafish reporter (top) and dichloro-dihydro-fluorescein diacetate treatment (bottom) showing the morphology of the whole intestines at 5 dpf (top) and 7 dpf (bottom). Scale bar: 200 μm. dpf: Days post fertilization.

The advantages of studying the lymphatic system in zebrafish[100] are well recognized, and recent studies using zebrafish models have shed light on IBD and drug development[101]. Our work on the zebrafish Feingold syndrome 1 model showed that Mycn loss-of-function leads to severe intestinal developmental defects resulting from proliferation arrest caused by abnormal ribosome biogenesis, which can be rescued through the mTOR pathway with leucine supplementation[102]. Similar to other vertebrates, zebrafish harbor commensal bacteria within their digestive tracts, and the use of gnotobiotic techniques allows for the study of microbial-host interactions. The importance of intestinal alkaline phosphatase in promoting mucosal tolerance to commensal bacteria by dephosphorylating and detoxifying the endotoxin component of lipopolysaccharide was first identified in a zebrafish model[103]. However, despite the accumulation of preliminary data, zebrafish have seldom been used to study CD because CD is not recognized as the intestinal manifestation of a pan-lymphatic disease. Therefore, our proposal may encourage the increased use of powerful zebrafish models for the study of CD.

A zebrafish model of IBD has been established through drug treatment and genetic modifications. Treating zebrafish embryos at 3-6 d post fertilization with 2,4,6-trinitrobenzene sulfonic acid (TNBS), DSS, or nonsteroidal anti-inflammatory drugs can result in bacterial overgrowth, neutrophil infiltration into the gut, upregulation of pro-inflammatory genes, or disruption of epithelial barrier function[104]. Zebrafish lacking macrophage-stimulating protein (MSP) develop spontaneous intestinal inflammation, which supports human genome-wide association study data showing that MSP is an IBD susceptibility factor[105]. Recent research has shown that PI3K deficiency in zebrafish can induce IBD-like features

with intestinal injury and inflammation, as well as the suppression of barrier-function-related IBD susceptibility genes [106]. Another study showed that Trmt5-deficient zebrafish spontaneously develop an IBD-like phenotype, including epithelial destruction, goblet cell failure, and an overactive immune system[107]. These zebrafish IBD models not only provide a better understanding of the pathological processes involved in IBD, but also provide powerful models for screening potential drug treatments. Combining publicly available databases, zebrafish chemical screening, machine learning, and mouse preclinical models, a recent study identified environmental factors that control intestinal inflammation, and revealed that the AHR-NF-κB-C/EBPβ signaling axis in T cells and DCs promotes intestinal inflammation and can be targeted by propyzamide[108]. Overall, the use of zebrafish as a model has greatly accelerated the study of intestinal diseases and the identification of potential treatment strategies.

CLINICAL BENEFITS OF CONSIDERING CD AS THE INTESTINAL MANIFESTATION OF PAN-LYMPHATIC DYSFUNCTION

The acknowledgment of CD as the intestinal manifestation of pan-lymphatic dysfunction may lead to the development of novel treatments targeting the lymphatic system. Studies targeting the lymphatic system are summarized in Tables 1 and 2[55,60,71,76,109-116]. Owing to the significant role of VEGFC-VEGFR3 signaling in lymphangiogenesis, VEGFC administration enhances lymphatic function and ameliorates acute and chronic colitis in animal models[60,117]. However, another study showed that Cartilage Oligomeric Matrix Protein – Angiopoietin-1 (COMP-Ang1) treatment alleviated DSS-induced colitis by diminishing inflammation-associated lymphangiogenesis and reducing macrophage infiltration, which are involved in the inhibition of VEGF-C and VEGF-D expression[109]. Moreover, a study showed that artemisinin ameliorated inflammation-induced lymphangiogenesis through the VEGF-C/VEGFR3 pathway and reduced colitis in animal models[110]. Therefore, the specific role of lymphangiogenesis in CD requires further investigation. Disruption of PBT is another treatment option for CD, and agents aimed at lymphocyte trafficking may have wide applicability[7]. Ozanimod, a new drug targeting the S1P1/5 receptor, significantly reduced the severity of colitis in mice treated with TNBS[118] and also successfully completed phase 2 clinical trials in patients with IBD[75,76]. In addition, phase 2/3 clinical trials of etrasimod, a S1P1/4/5 receptor modulator, are underway in patients with CD (NCT04173273). Considering the concept of pan-lymphatic dysfunction, disrupting lymphocyte trafficking *via* the S1P pathway may be crucial. TLR4 has been shown to play several roles within mesenteric lymphatic vessels, and its inhibitor C34 significantly reduced the severity of DSS-induced colitis in a mouse model[71]. In addition, a study on the bacterial FimH blocker EB8018, which can inhibit the activation of TLR4, is ongoing (NCT03709628). Furthermore, an anti-*Mycobacterium Avium Ssp. Paratuberculosis* agent, RHB-104, showed a therapeutic effect in patients with CD, causing lower disease activity and reduced CD activity index scores (NCT03009396).

Antiplatelet agents could be promising targets for CD based on the involvement of platelets in intestinal inflammation. A previous study showed that an antiplatelet antibody, a GPIb inhibitor, ameliorated DSS-induced colitis by promoting lymphangiogenesis and increasing lymphatic vessel density[55]. Other therapeutic agents, such as Janus kinase inhibitors, anti-adhesion molecules, and anti-IL-1β/6/23, could impact the lymphatic system. However, it remains unclear whether changes observed in the lymphatic system are the cause or result of disease improvement. As MLNs are the primary site of CD pathogenesis, excision of MLNs, as well as the mesentery, has been correlated with decreased recurrence of ileocolic CD[27].

The clinical management of the long-term consequences of CD, such as intestinal fibrosis and obstruction, is challenging, and the lack of understanding of the underlying mechanisms has contributed to a shortage of effective therapies. It has been claimed that fibrosis in CD is a consequence of chronic gut edema, which may be caused by lymphatic dysfunction, as decreased lymph flow during chronic inflammation has been observed[119]. Additionally, fatty acids released from creeping fat have been reported to promote muscle proliferation[92], indicating a potential role of creeping fat in fibrosis and obstruction in CD. Therefore, treatments targeting lymphatic dysfunction offer a viable means of managing fibrosis in patients with CD.

CONCLUSION

Based on the evidence presented above, it is reasonable to conclude that the lymphatic system plays an active role in the pathogenesis, progression, and complications of certain diseases. Intriguingly, immune-mediated inflammatory diseases, including IBD, rheumatoid arthritis, and sclerosing cholangitis, emphasize the disease-driving mechanisms and therapeutic strategies shared by these diseases[39]. Similarly, the concept of CD as the intestinal manifestation of pan-lymphatic dysfunction may change our understanding of disease initiation, progression, and treatment. For instance, it has been shown that increased lymphatic vessel density could occur even in non-inflamed areas. Clinical management of the extraintestinal manifestations (EIMs) of CD has long been challenging[10]; the concept of pan-lymphatic dysfunction may provide a new perspective on EIM formation and management. However, unresolved problems require further investigation.

We propose this concept based on accumulating evidence of lymphatic system involvement in CD, including the existence of lymphatic system dysfunction, recognition of the inside-out model, disorders of immune cells, changes in cell plasticity, partial overlap of underlying mechanisms, and gut-derived fatty and bile acid metabolism. This hypothesis offers a larger potential role for zebrafish as a model of CD because of the ability to study lymphatic dysfunction in this

Table 1 Current studies (published articles and finished/on-going clinical trials) investigating the effect of targeting lymphatic circulation and related pathophysiology processes, providing strong evidence to support our hypothesis

Agent class	Agent	Mechanism/pathway	Drug stage	Efficacy	Ref.
Targets of lymphangiogenic factors	VEGFC/Ad-hVEGF-C	VEGFC-VEGFR3 signaling pathway; increase lymph drainage and bacteria antigen clearance	Animal model	Reduced severity of chronic colitis in terms of histological examination, body weight, endoscopic evaluation, and CDAI than control group	[60]
	COMP-Ang1	Reduce inflammation-induced lymphangiogenesis and M1 and M2 macrophage infiltration by inhibiting VEGF-C/D expression	Animal model	Less weight loss, fewer clinical signs of colitis, and longer colons than control group	[109]
TLR4 inhibitor	C34	TLR4-PAMP/DAMP discriminatory mechanism	Animal model	Less weight loss, reduced disease activity score and reduced colon shortening in treatment group	[71]
Anti-trafficking therapies: S1P receptor modulators	Ozanimod	S1P1/5 receptor modulator; induce internalization and degradation of S1P1/5 receptor subtypes	Phase 2 clinical studies in patients with CD	Endoscopic, histological, and clinical improvements within 12 wk of initiating ozanimod therapy in patients with moderate to severe CD	[76]
			Phase 3 clinical studies	Recruiting	NCT03440372, NCT03440385, NCT03464097, NCT03467958
	Etrasimod	S1P1/4/5 receptor modulator	Phase 2/3 clinical studies in patients with CD	Recruiting	NCT04173273
Antiplatelet antibody	GPIb inhibitor	Promote lymphangiogenesis and increase lymphatic vessel densities	Animal model	Suppressed colitis with reduced thickness of the submucosal layer, reduced inflammatory cell infiltration, and reduced histological score	[55]
Anti-bacterial and its related metabolites or secretions[1]	EB8018	Inhibit bacterial lectin (FimH) to stop the activation of TLR4 and ensuing TNF-α production	Open-label, multicenter, pharmacokinetic Study	Finished without results disclosure	NCT03709628
	RHB-104	Anti-MAP (Mycobacterium Avium Ssp. Paratuberculosis	Phase 3 study to assess the efficacy and safety of fixed-dose combination RHB-104	Number of patients in remission at week 16 was higher in RHB-104 compared with placebo	NCT03009396
			A randomized, double blind, placebo-controlled, multicenter, parallel group study	Reduction of the total CDAI score to less than 150 at week 26 was significantly higher in RHB-104 than placebo	NCT01951326
Chemical compound	Artemisinin	Ameliorate inflammation-driven lymphangiogenesis *via* the VEGFC/VEGFR3 signaling pathway	Animal model	Reduced symptoms of colitis with improved tissue histology, relieved inflammatory edema, and decreased infiltration of inflammatory cells	[110]

[1]These studies specifically support the inside-out model of the pathogenesis of Crohn's disease.

CD: Crohn's disease; CDAI: Crohn's disease activity index; COMP-Ang1: Cartilage Oligomeric Matrix Protein – Angiopoietin-1; DAMP: damage-associated molecular pattern; PAMP: Pathogen-associated molecular pattern; S1P: Sphingosine-1-phosphate; TLR: Toll-like receptor; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor.

model. Importantly, the ensuing focus on improving lymphatic function may lead to the development of novel therapeutic strategies and improve the clinical management of patients with CD.

Table 2 Current studies (published articles and finished/on-going clinical trials) investigating the effect of targeting lymphatic circulation and related pathophysiology processes, providing moderately strong evidence to support our hypothesis

Agent class	Agent	Mechanism/pathway	Drug stage	Efficacy	Ref.
JAK inhibitors	Filgotinib/GLPG0634	Selective JAK1 inhibitor; inhibiting JAK-STAT pathway	Phase 2 clinical studies in patients with CD	Filgotinib induced clinical remission in significantly more patients with active CD compared with placebo (47% *vs* 23%)	[111]
			Phase 3 clinical studies	Recruiting or finished without result disclosure	NCT02914600, NCT02914561, NCT02048618
	MT-1303	Selective JAK1 inhibitor; inhibiting JAK-STAT pathway	Phase II, open-label, multicenter studies for moderate to severe active CD	Finished without results disclosure	NCT02389790, NCT02378688
	Upadacitinib[1]	Selective JAK1 inhibitor; Inhibiting JAK-STAT pathway	Multicenter, randomized, double-blind, placebo-controlled induction study of its efficacy and safety in moderate to severe active patients with CD	Upadacitinib induced CDAI remission at week 12 in significantly more patients with active CD compared with placebo (49.5% *vs* 29.1%)	NCT03345849, NCT03345836
Anti-trafficking therapies: target of adhesion molecules	AS101	Inhibit lymphocyte trafficking by blocking ligand for α4β7 integrin, MAdCAM-1 and Il-1β. Regulate the intestinal epithelial barrier by the PI3K/AKT pathway	Animal model	Suppressed colitis with reduced colonic inflammatory cytokine levels, reduced histopathology score and fewer clinical symptoms	[112]
	Vedolizumab	Inhibit lymphocyte trafficking by block the ligand for α4β7 integrin, MAdCAM-1	Induction and maintenance study for active CD	The rate of clinical remission is significantly higher in treatment group (300 mg) at week 6	[113]
	Firategrast	α4β7 and α1β7 inhibitor	Randomized, double-blind, placebo-controlled, parallel-group study	Finished without results disclosure	NCT00101946
	Abrilumab	Inhibit lymphocyte trafficking by blocking the ligand for α4β7 integrin, MAdCAM-1	Phase 1, randomized, double-blind, placebo-controlled, ascending multiple dose study	Finished without results disclosure	NCT01290042
	CCX282-B	Anti CCR9 and its related Ca^{2+} mobilization and inflammatory cell attraction	Pilot, double-blind, placebo-controlled, parallel group study	Finished without results disclosure	NCT00102921
	Risankizumab	Monoclonal antibody against the p19 subunit of IL-23	Phase 2 clinical studies in patients with CD	Effective in clinical remission, response, and endoscopic remission at week 12 compared to placebo	[114,115] NCT03105128
IL-23 inhibitors	Ustekinumab	Monoclonal antibody against p40 subunit of IL-12/IL-23	Induction and maintenance study for active CD	Rate of response was significantly higher in treatment group (dosage as 130 mg or 6 mg/kg) in both UNITI 1 and UNITI	[116]
	Brazikumab	Monoclonal antibody against the p19 subunit of IL-23	Phase 1 clinical trial in healthy people	Finished without results disclosure	NCT05033431
Other IL inhibitors	Semapimod	IL-1β/IL-6 inhibitors	Open label single arm study for CD	Finished without results disclosure	NCT00740103

[1]There are two clinical trials on upadacitinib from the same leading team but with different designs and recruiting patient numbers. For the word limitations of this article, please refer to the relative number of clinical trials required.

CD: Crohn's disease; CDAI: Crohn's disease activity index; IL: Interleukin; JAK: Janus kinase; MAdCAM: Mucosal vascular addressin cell adhesion molecule; PI3K: Phosphoinositide 3-kinase.

FOOTNOTES

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