

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2021 December 27; 13(12): 1523-1769



FRONTIER

- 1523 Photodynamic therapy: A next alternative treatment strategy for hepatocellular carcinoma?
Zhu F, Wang BR, Zhu ZF, Wang SQ, Chai CX, Shang D, Li M

REVIEW

- 1536 Role of mesenteric component in Crohn's disease: A friend or foe?
Yin Y, Zhu ZX, Li Z, Chen YS, Zhu WM
- 1550 Neoadjuvant treatment strategies for hepatocellular carcinoma
Xu L, Chen L, Zhang W
- 1567 Mucinous adenocarcinoma: A unique clinicopathological subtype in colorectal cancer
Huang A, Yang Y, Shi JY, Li YK, Xu JX, Cheng Y, Gu J

MINIREVIEWS

- 1584 Endoscopic therapy of weight regain after bariatric surgery
Bulajic M, Vadalà di Prampero SF, Bošković I, Costamagna G
- 1597 Patient-centered developments in colon- and rectal cancer with a multidisciplinary international team: From translational research to national guidelines
Link KH, Kornmann M, Staib L, Kreuser ED, Gaus W, Röttinger E, Suhr P, Maulbecker-Armstrong C, Danenberg P, Danenberg K, Schatz M, Sander S, Ji ZL, Li JT, Peng SY, Bittner R, Beger HG, Traub B
- 1615 Advances in liver transplantation for unresectable colon cancer liver metastasis
Cui X, Geng XP, Zhou DC, Yang MH, Hou H

ORIGINAL ARTICLE**Retrospective Study**

- 1628 Pediatric T-tube in adult liver transplantation: Technical refinements of insertion and removal
Spoletini G, Bianco G, Franco A, Frongillo F, Nure E, Giovinozzo F, Galiandro F, Tringali A, Perri V, Costamagna G, Avolio AW, Agnes S
- 1638 Preoperative calculation of angles of vision and working area in laparoscopic surgery to treat a giant hiatal hernia
Lara FJP, Zubizarreta Jimenez R, Moya Donoso FJ, Hernández Gonzalez JM, Prieto-Puga Arjona T, del Rey Moreno A, Pitarich Martinez M
- 1651 Effect of aluminum phosphate gel on prevention of early rebleeding after ligation of esophageal variceal hemorrhage
Zhang ZL, Peng MS, Chen ZM, Long T, Wang LS, Xu ZL

- 1660** Postoperative complications after robotic resection of colorectal cancer: An analysis based on 5-year experience at a large-scale center

Huang ZX, Zhou Z, Shi HR, Li TY, Ye SP

- 1673** 'Short' pancreaticojejunostomy might be a valid option for treatment of chronic pancreatitis in many cases

Murruste M, Kirsimägi Ü, Kase K, Veršinina T, Talving P, Lepner U

- 1685** Risk factors for perioperative complications in laparoscopic surgeries of retrorectal cystic lesions

Wang PP, Lin C, Zhou JL, Xu KW, Qiu HZ, Wu B

- 1696** Liver resection *vs* radiofrequency ablation in single hepatocellular carcinoma of posterosuperior segments in elderly patients

Delvecchio A, Inchingolo R, Laforgia R, Ratti F, Gelli M, Anelli MF, Laurent A, Vitali G, Magistri P, Assirati G, Felli E, Wakabayashi T, Pessaux P, Piardi T, di Benedetto F, de'Angelis N, Briceño J, Rampoldi A, Adam R, Cherqui D, Aldrighetti LA, Memeo R

Observational Study

- 1708** Expression of adipokine ghrelin and ghrelin receptor in human colorectal adenoma and correlation with the grade of dysplasia

Stojavljevic-Shapeski S, Virovic-Jukic L, Tomas D, Duvnjak M, Tomasic V, Hrabar D, Kralj D, Budimir I, Barsic N, Ljubcic N

SYSTEMATIC REVIEWS

- 1721** Right sided diverticulitis in western countries: A review

Epifani AG, Cassini D, Ciocchi R, Accardo C, Di Candido F, Ardu M, Baldazzi G

- 1736** Platelet rich plasma effectiveness in bowel anastomoses: A systematic review

Geropoulos G, Psarras K, Giannis D, Martzivanou EC, Papaioannou M, Kakos CD, Pavlidis ET, Symeonidis N, Koliakos G, Pavlidis TE

- 1754** Current and future role of three-dimensional modelling technology in rectal cancer surgery: A systematic review

Przedlacka A, Pellino G, Fletcher J, Bello F, Tekkis PP, Kontovounisios C

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Marcello Donati, FACS, MD, PhD, Professor, Department of Surgery and Medical-Surgical specialties, University of Catania, Catania 95125, Italy. mdonati@unict.it

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS, World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJGS* as 2.582; IF without journal self cites: 2.564; 5-year IF: 3.378; Journal Citation Indicator: 0.53; Ranking: 97 among 212 journals in surgery; Quartile category: Q2; Ranking: 73 among 92 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Rui-Rui Wu, Production Department Director: Xiang Li, Editorial Office Director: Ya-Juan Ma.

NAME OF JOURNAL

World Journal of Gastrointestinal Surgery

ISSN

ISSN 1948-9366 (online)

LAUNCH DATE

November 30, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Shu-You Peng, Varut Lohsirivat

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9366/editorialboard.htm>

PUBLICATION DATE

December 27, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Role of mesenteric component in Crohn's disease: A friend or foe?

Yi Yin, Zhen-Xing Zhu, Zhun Li, Yu-Sheng Chen, Wei-Ming Zhu

ORCID number: Yi Yin 0000-0002-9745-1363; Zhen-Xing Zhu 0000-0001-6948-9770; Zhun Li 0000-0003-0968-3031; Yu-Sheng Chen 0000-0002-6617-3356; Wei-Ming Zhu 0000-0002-5841-3655.

Author contributions: Yin Y and Zhu ZX contributed equally to this work; Yin Y and Zhu ZX designed and wrote the final version of the manuscript; Li Z and Chen YS were critical for the acquisition of data and drafting the manuscript; Zhu WM made critical revisions to the design and gave final approval for the article to be submitted.

Conflict-of-interest statement: All authors declare no conflicts of interest for this article.

Country/Territory of origin: China

Specialty type: Pathology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and

Yi Yin, Zhen-Xing Zhu, Zhun Li, Yu-Sheng Chen, Wei-Ming Zhu, Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, Nanjing 210002, Jiangsu Province, China

Corresponding author: Wei-Ming Zhu, MD, PhD, Chief Doctor, Professor, Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, No. 305 East Zhongshan Road, Nanjing 210002, Jiangsu Province, China. drweimingzhu@126.com

Abstract

Crohn's disease (CD) is a complex and relapsing gastrointestinal disease with mesenteric alterations. The mesenteric neural, vascular, and endocrine systems actively take part in the gut dysbiosis-adaptive immunity-mesentery-body axis, and this axis has been proven to be bidirectional. The abnormalities of morphology and function of the mesenteric component are associated with intestinal inflammation and disease progress of CD *via* responses to afferent signals, neuropeptides, lymphatic drainage, adipokines, and functional cytokines. The hypertrophy of mesenteric adipose tissue plays important roles in the pathogenesis of CD by secreting large amounts of adipokines and representing a rich source of proinflammatory or profibrotic cytokines. The vascular alteration, including angiogenesis and lymphangiogenesis, is concomitant in the disease course of CD. Of note, the enlarged and obstructed lymphatic vessels, which have been described in CD patients, are likely related to the early onset submucosa edema and being a cause of CD. The function of mesenteric lymphatics is influenced by endocrine of mesenteric nerves and adipocytes. Meanwhile, the structure of the mesenteric lymphatic vessels in hypertrophic mesenteric adipose tissue is mispatterned and ruptured, which can lead to lymph leakage. Leaky lymph factors can in turn stimulate adipose tissue to proliferate and effectively elicit an immune response. The identification of the role of mesentery and the crosstalk between mesenteric tissues in intestinal inflammation may shed light on understanding the underlying mechanism of CD and help explore new therapeutic targets.

Key Words: Crohn's disease; Mesenteric nerves; Angiogenesis; Lymphatic drainage; Mesenteric adipose tissue

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Received: January 29, 2021

Peer-review started: January 29, 2021

First decision: July 29, 2021

Revised: August 1, 2021

Accepted: November 25, 2021

Article in press: November 25, 2021

Published online: December 27, 2021

P-Reviewer: Fonseca-Alves CE

S-Editor: Ma YJ

L-Editor: Filipodia

P-Editor: Ma YJ



Core Tip: Crohn's disease (CD) is a complex autoimmune disease with increasing incidence worldwide, especially in Asian countries in recent years. There has been excellent progress in understanding the role of the mesentery in the pathogenesis and disease progress of CD. The crosstalk between components and intestinal inflammation has aroused many researchers' interests. Herein, we will discuss the basic function and the alteration under inflammatory state of mesenteric nerves, blood vessels, lymphatics, and fat mass. Existing therapeutic strategies associated with mesentery components will also be summarized.

Citation: Yin Y, Zhu ZX, Li Z, Chen YS, Zhu WM. Role of mesenteric component in Crohn's disease: A friend or foe? *World J Gastrointest Surg* 2021; 13(12): 1536-1549

URL: <https://www.wjgnet.com/1948-9366/full/v13/i12/1536.htm>

DOI: <https://dx.doi.org/10.4240/wjgs.v13.i12.1536>

INTRODUCTION

Crohn's disease (CD) is a chronic relapsing autoimmune disease that can affect the entire gastrointestinal tract and is mainly characterized by segmental intestinal inflammation[1]. The mesentery is now well recognized as the collection of tissues that maintains all abdominal digestive organs in position and in continuity with other systems. The mesentery is made up of adipose tissue, a connective tissue matrix, nerve tissue, lymphatics, blood vessels, and immune cells[2-4]. The macroscopic lesions of mesentery including thickening, stiff, and hypertrophy are hallmarks of CD[5,6]. The histopathological findings of the mesentery from patients with CD demonstrates fibrosis, dilated lymphatic vessels (LV), perivascular inflammation, perineuronal chronic inflammation, and small-sized adipocytes[7,8]. However, the role and the involvement of the mesentery in the pathogenesis and clinical course of CD is still unclear and controversial. Some research points to the mesentery as a protective organ, able to mount a controlled inflammatory response following abnormal intestinal bacterial translocation[9,10]. On the opposing side, there is evidence suggesting that the participation and involvement of the mesentery in the setting of CD is negative, fueling the pathogenesis of the disease[11]. This review aims to describe the role of mesenteric nerves, lymphatics, blood vessels, and adipose tissue in the systemic and local inflammation in CD. Recent studies and progress on this topic will be reviewed to investigate the relationship between the mesentery and disease course of CD and the potential therapeutic target for CD treatment.

NERVES

There have been several studies indicating the involvement of the neuroendocrine and enteric nervous system in CD[12]. However, the role of mesenteric nerves in the pathogenesis and prognosis of CD is still unclear. In fact, as a vital part of the brain-gut axis, the mesenteric nerves provide a physiological link between the central nerve system and gastrointestinal tract[13]. Based on anatomical considerations, the mesenteric nerves include the vagal and sympathetic nerves. The vagus nerve (VN) is the main component of the parasympathetic nerve system, which is composed of afferent and efferent fibers[14]. Peripheral sensations can be integrated into the central autonomic network *via* vagal afferents, and then the efferent response of the VN is able to modulate gastrointestinal nociception and inflammation[15]. The sympathetic nerve enters the intestinal tract along with the artery and terminates in the enteric nervous system, innervating the intestinal layers and intestinal associated lymphoid tissue[16, 17].

Previous studies have confirmed that vagal and sympathetic nerves play an important role in regulating inflammation[18]. In trinitrobenzene sulfonic acid-induced colitis and acetic acid-induced colitis mice models, hyperexcitable visceromotor neurons were observed in the inferior mesenteric ganglia[19]. A recent animal experiment also confirmed that vagotomy increased the susceptibility to colitis in mice, mainly by inhibiting the alpha7 nicotinic acetylcholine receptors-mediated cholinergic anti-inflammatory pathway[20], whereas treatment with nicotine (alpha7

nicotinic acetylcholine receptors agonist) and galantamine (cholinesterase inhibitors) was shown to reverse the severity of colitis induced by dextran sulfate sodium[21,22]. In addition, another study found that vagal innervation was involved in the formation of tertiary lymphoid tissue in colitis, which is lymphoid tissue that forms as a result of chronic inflammation in a tissue or organ[23]. Unfortunately, the role of this lymphoid tissue in inflammatory bowel disease (IBD) remains unclear. Similarly, sympathectomy aggravated colitis (induced by dextran sulfate sodium or *via* T cell transfer) in mice. It was also observed in this experiment that intestine-specific vagal nerve denervation had no effect in dextran sulfate sodium-induced colitis[24]. Meanwhile, some researchers proved that the sympathetic nerve played a pivotal role in inhibiting innate immune cells against microorganism, likely *via* the adrenergic β_2 receptor[25], which not only inhibited the secretion of tumor necrosis factor alpha (TNF α) but also drove rapid interleukin (IL)-10 secretion from innate cells[26]. In addition, several studies have shown that anxiety and depression can interact with intestinal inflammation through the bidirectionality of the brain-gut axis in patients with IBD[27]. The positive implementation of psychological intervention in patients with CD can alleviate the changes of their condition[28]. Therefore, we have reasons to believe that the pathogenesis of CD is closely related to the changes of mesenteric nerves.

Indeed, the tone of the vagus system is altered in patients with CD[29]. A matched cohort study for nearly 60 years found a positive correlation between vagotomy and IBD, especially in CD patients, which indirectly highlighted the beneficial role of vagal tone in intestinal inflammation[30]. A study has also confirmed that the sympathetic innervation of intestinal mucosa and the catecholamine neurotransmitters released by sympathetic nerve in CD patients decreased[31]. Interestingly, as a form of IBD, ulcerative colitis (UC) was not associated with the loss of sympathetic nerve fibers. By contrast, increased density of the sympathetic nerve network was found in UC patients[32]. Thus, the underlying mechanism of CD and UC seems different in intestinal immunity regulated by sympathetic nerves. Based on these studies, a research group conducting a clinical trial of VN stimulation in patients with active CD reported clinical, biological, and endoscopic remission in 5 of 7 patients treated with VN stimulation and restored vagal tone[33].

In summary, the mesenteric nerves have been proven to be involved in the bidirectional regulation of inflammation and emotion of the brain-gut axis and in the pathogenesis of CD. The clinical trials with VN stimulation intervention provide a new target for CD treatment. Meanwhile, drugs targeting neurotransmitter receptors also seem promising and worth exploring. Anti-depression treatment helps decrease the mesenteric afferent nerve activity and further ameliorates intestinal inflammation, which can be a potential therapeutic target for CD treatment.

BLOOD VESSELS

The abnormality of mesenteric blood supply in CD has been confirmed, although the underlying mechanism is not well clarified. Histopathological features of injured blood vessels, including vascular injury, focal arteritis, fibrin deposition, arterial occlusion, and even granulomatous vasculitis, are observed in diseased segment in CD [34,35]. Meanwhile, the microvascular dysfunction was found to be correlated with disease activity and relapse of CD[36,37]. Radiological evidence of mesenteric hypervascularity (also known as the “comb sign”) coupled with radiological evidence of nodal enlargement is associated with endoscopic evidence of mucosal ulceration [38]. The association between splanchnic hemodynamics and disease activity of CD has also been investigated by Doppler sonography[39]. Of note, the superior mesenteric artery flow has been accessed for Crohn's ileitis diagnosis and for disease activity monitoring[40,41]. The velocity of blood flow in the superior mesenteric artery was markedly higher in CD patients compared to controls. By contrast, the resistance index of the superior mesenteric artery was lower in active CD than controls[42,43]. The cumulative clinical evidence suggests that the function of vasculature is altered in CD.

Angiogenesis is an important component of CD pathogenesis. Molecular studies have confirmed that angiogenesis is crucial to inflammation and is associated with activation and proliferation of endothelial cells and capillary and venule remodeling, resulting in an expansion of the tissue microvascular bed[44-46]. A potential consequence of this expansion is notable promotion of inflammation through various cytokines, chemokines, and matrix metalloproteinases[47,48]. The involvement of hypoxia inducible factor (HIF) has been extensively studied. Increased expression of

HIF-1 and HIF-2 has been detected in inflamed tissue of IBD patients[49]. Importantly, HIF stimulates angiogenesis *via* vascular endothelial growth factor (VEGF) induction [50]. Of note, VEGF-A is markedly increased in the tissue and serum of patients with CD[51-53] and is implicated in angiogenesis in experimental colitis[54]. The importance of the VEGF family proteins in the pathogenesis and disease course of IBD has also been demonstrated in studies assessing the efficacy of different therapeutic regimens for IBD. Recently, Algaba *et al*[55] found that circulating levels of VEGF-A significantly decreased after anti-TNF- α therapy and that elevated VEGF-A levels at baseline might predict a poor response to TNF- α inhibitors.

Endothelial cell adhesion molecules also play an important role in vascular proliferation through recruitment of inflammatory cells to the site of inflamed intestine. The activated vascular endothelial cells express several cell adhesion molecules, which are essential for the regulation of leukocyte trafficking and migration[56]. Three main families of cell adhesion molecules and their ligands (selectins, integrins, and immunoglobulin superfamily) are engaged in the process. The binding of the integrins $\alpha 4\beta 7$ and $\alpha 4\beta 1$ on leukocytes to their ligands on the endothelial cells, mucosal addressin cell adhesion molecule-1 (MadCAM-1) and vascular CAM-1, seem to be one of the most important interaction[57]. Previous studies have proved that mucosal addressin CAM-1 is overexpressed on intestinal high endothelial venules during active IBD, which promotes homing and tethering of inflammatory cells[57,58]. Anti-integrin therapeutics, including gut-selective antibodies against the $\beta 7$ integrin subunit (etrolizumab) and the $\alpha 4\beta 7$ integrin heterodimer (vedolizumab and abrilumab), the non-gut selective anti- $\alpha 4$ integrin (natalizumab), as well as small molecules (AJM300) were developed for IBD treatment. Among which, vedolizumab and etrolizumab demonstrate similar inhibition of dynamic adhesion of lymphocytes from IBD patients to mucosal addressin CAM-1.

The abnormal upregulation of endothelial cell adhesion molecules and increased adhesion of leukocytes likely result in coagulation abnormalities. In fact, CD patients are at high risk of developing mesenteric thrombosis[59,60]. Among patients with CD, mesenteric venous thrombosis is associated with bowel stenosis and CD-related intestinal surgery[60]. Purposed risk factors also include the use of conjugated estrogens, surgery-associated trauma, intestinal stricture, pregnancy, and history of blood clot[61]. As aforementioned, anti-adhesion molecule therapy, which deters leukocyte recruitment, has been shown to be effective in the treatment of CD. The clinical evidence has confirmed angiogenesis as a component of CD[62] and angiogenesis blockade as a new therapeutic approach to experimental colitis[63].

LYMPHATICS

Although the pathophysiology of CD remains unknown, the involvement of the lymphatic system in CD has long been suggested. Abnormal lymphatics, such as lymphangiogenesis and enlarged and obstructed LVs, has been described in CD patients and is likely related to early onset submucosa edema (Figure 1)[64]. It is reported that intestinal granulomas[65], granulomas in the mesenteric lymph nodes, decreased intestinal, and mesenteric LV density[66] are associated with the postoperative recurrence of CD.

Lymph flow plays an important role in transporting antigens, dendritic cells, and macrophages[67,68]. Many studies have reported that lymphatic dysfunction can lead to immunosuppression[69,70]. It is believed that lymph flow is enhanced during an inflammatory state. However, inflammation may in turn impair lymphatic pumping with lymphatic obstruction and impaired lymphatic contraction, leading to a poor drainage of interstitial fluid[71,72]. It is well-known that inflammatory mediators, such as prostaglandins and cytokines, can increase vascular permeability, causing submucosal edema. These inflammatory mediators play a potential role in altering LV contractions and lymph flow during their transport from inflammatory tissues to draining lymph nodes, impairing immune response[72]. Rahier *et al*[73] reported that the LV density increased in inflammatory bowel disease. One possible reason for the lymphangiogenesis may be contributing to improved lymphatic drainage in response to mesenteric lymphatic obstruction, marked lacteal dilatation, and extensive submucosal edema[72].

The molecular underlying mechanism of lymphangiogenesis in CD patients remains largely unknown. Many factors are involved in lymphangiogenesis, such as members of the VEGF family, hepatocyte growth factor, insulin-like growth factor-2, platelet-derived growth factor-BB, and fibroblast growth factor-2[74-77]. VEGF-C and VEGF-D

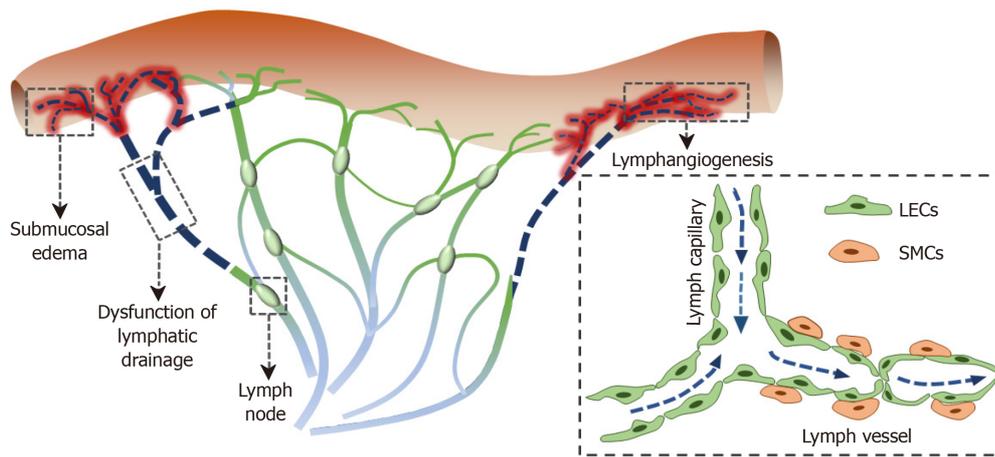


Figure 1 Alteration of both structures and functions of mesenteric lymphatic vessels aggravates intestinal inflammation in Crohn's disease. LECs: Lymphatic epithelial cells; SMCs: Smooth muscle cells.

are members of the VEGF family, which mediate lymphangiogenesis *via* their receptor VEGFR3[78]. The blockade of the VEGFR3 signaling pathway can suppress lymphangiogenesis and further aggravate intestinal inflammation. Of note, lymphangiogenic factor VEGF-C has shown promising therapeutic effects in experimental colitis, both clinically and histologically[79]. These studies suggest that mesenteric lymphatics may be a promising potential target for CD treatment. Recently, we found that intestinal inflammation was significantly improved by the application of lymphatics-targeting drug release in the IL-10^{-/-} spontaneous experimental colitis, suggesting that mesenteric LVs are potential targets for CD treatment[80].

The lymphoid aggregates resembling tertiary lymphoid organs, composed of CD3⁺ T cells surrounding CD20⁺ B cell clusters, have been observed in the mesentery of CD patients[81-83]. Guedj *et al*[81] recently proposed a notion that mesenteric adipose cells can participate in the process of tertiary lymphoid organ formation in the creeping fat of CD-affected mesentery. In addition, lymphoid cells invade the LV wall in CD-affected mesentery, suggesting the involvement of tertiary lymphoid organs in the lymphatic remodeling[82]. The lymphatic remodeling includes lymphangiogenesis, LV dilation, and lymph leakage. Interestingly, the lymph leakage in surrounding mesenteric adipose tissue can stimulate the growth of adipose tissue. The leaky antigens, lipids, and cytokines released from adipose cells can effectively promote immune response[84].

As described above, increased LV density in the intestinal wall has been found in CD patients. Recently, a study has found that decreased LV density in intestinal mucosa is associated with higher risk of endoscopic recurrence after surgical intervention[85], suggesting that increased LV density may contribute to reduced recurrence of CD, which was consistent with the notion that increased lymphangiogenesis could be a compensatory response to lymphatic dysfunction. By contrast, the results reported by Li *et al*[66] showed that increased mesenteric LV density in the proximal margin was associated with higher risk of early clinical recurrence after surgery in CD patients. One possible reason for the difference is that the locations of the LV densities were different.

Granulomas are observed only in some patients with CD (less than 13%), and they are associated with a more aggressive disease phenotype of CD[86]. In this case, patients with granulomas, who have undergone surgery for CD, have a higher risk for reoperation[86]. Of note, Li *et al*[87] reported that the presence of granulomas in mesenteric lymph nodes instead of the granulomas in the intestine is an independent risk factor for postoperative recurrence in CD patients. In conclusion, accumulating studies have demonstrated the involvement of the lymphatic system in CD. Although the underlying mechanism of the alterations of mesenteric lymphatics is not well clarified, promoting lymphatic function in CD patients could improve prognosis.

ADIPOSE TISSUE

Mesenteric adipose tissue hypertrophy is regarded as a feature of CD and was firstly

reported by Dr. Burrill B. Crohn himself to be a consistent symptom of the disease[8]. The pathologically altered mesenteric fat tissue is called "creeping fat," defined as expansion of mesenteric adipose tissue around the inflamed and fibrotic intestine (Figure 2)[5]. The creeping fat takes place at the mesenteric transition zone, where the intestinal wall and mucosa change synchronizing with the mesentery[88]. Additionally, creeping fat has been used as an anatomical marker for surgeons to determine the margin of resection during surgery[89]. Meanwhile, a number of studies revealed that creeping fat might play an important role in the pathogenesis of CD, by secreting large amounts of adipokines and representing a rich source of TNF, IL-6, IL-10, and other proinflammatory or profibrotic cytokines[90].

It has been demonstrated that adipokines are strongly associated with severity of intestinal inflammation. However, their exact role in the pathogenesis and disease course of IBD has not been concluded. Herein, we are discussing three important adipokines (adiponectin, leptin, and apelin) and their roles in the crosstalk with intestinal inflammation.

Adiponectin is a well-explored adipokine and plays a key role in regulating insulin sensitivity[91]. According to previous studies, adiponectin is markedly upregulated in the creeping fat of CD compared to the non-creeping fat of CD, UC, and healthy controls[92]. Its molecular architecture is strikingly similar to that of TNF- α in the terminal structure of the globular domain, despite lacking homology in the primary sequence[93]. Therefore, adiponectin presents an anti-inflammatory effect based on the antagonistic effect of TNF- α [94]. On the other hand, it is demonstrated that adiponectin inhibits the expression of adhesion molecules, metalloproteinases, and proinflammatory mediators[95].

Leptin is mainly secreted by white adipose tissue and regulates the differentiation, function, and metabolism of a variety of immune cell subpopulations and intestinal epithelial cells[96-98]. Previous studies described that leptin expression was upregulated in the mesenteric tissue of CD patients[99]. It has been shown that leptin modulates intestinal inflammation in experimental colitis[100]. Moreover, several studies have demonstrated that leptin deficiency and the pharmacologic blockade of the leptin receptor notably ameliorate colitis[101]. Leptin promotes T cell proliferation, resulting in an increased production of type 1 T helper cell-related cytokines[98]. A recent study revealed that leptin was crucial to human immune homeostasis and contributed to autoimmunity in a TNF α -dependent manner[102].

Apelin induces proliferation of intestinal epithelial cells[103]. Meanwhile, it was revealed that apelin plays a significant role in the development and stabilization of LVs[104,105]. Ge *et al*[106] reported that apelin was highly expressed in the mesenteric fat and in colon tissues of CD patients, which strongly suggested that apelin may ameliorate intestinal inflammation by enhancing lymphatic drainage. Han *et al*[103] indicated that the intraperitoneal injection of apelin-13 decreased mucosal inflammation, inhibited the infiltration of inflammatory cells, and decreased expression of proinflammatory cytokine mRNA levels in the murine colonic tissue. Exogenous apelin can also enhance tissue repair by increasing the colonic epithelial cell proliferation[103].

As aforementioned, leptin promotes the M2 macrophage subtype and subsequently enhances fibrosis by secreting large amounts of profibrotic factors such as tumor growth factor- β [107,108]. Meanwhile, Rieder *et al*[109] observed that creeping fat derived mediators such as free fatty acids (FFAs), induced a differential and selective proliferative response by human intestinal fibroblast and human intestinal muscle cells. FFA can promote the proliferation of human intestinal muscle cells and human intestinal fibroblasts rather than increase the proliferation of epithelial cells, endothelial cells, or adipocytes. This suggests that the proliferation induced by FFAs is intestinal mesenchymal cell specific. The proliferation induced by long-chain FFAs is dependent on the kinases p38 mitogen-activated protein kinase, protein kinase C, and phosphoinositide 3-kinase[109]. These studies suggest that creeping fat correlates with the stricture formation.

Bacteria translocate from the intestine to the mesentery through transmural inflammation in CD, largely resulting from impaired epithelial integrity[110]. Adipocytes and pre-adipocytes in the mesenteric fat express functional pattern recognition receptors, such as toll-like receptors and nucleotide oligomerization domain receptor-1 [111-114]. These receptors respond to the translocated bacteria by sensing microbe-derived molecules[10]. The downstream signaling cascade leads to activation of transcription factors (such as nuclear factor- κ B) and induction of proinflammatory cytokines and chemokines[115]. Moreover, pre-adipocytes can differentiate into macrophages and then modulate the inflammatory reaction, including phagocytic activity and proinflammatory cytokine release[116].

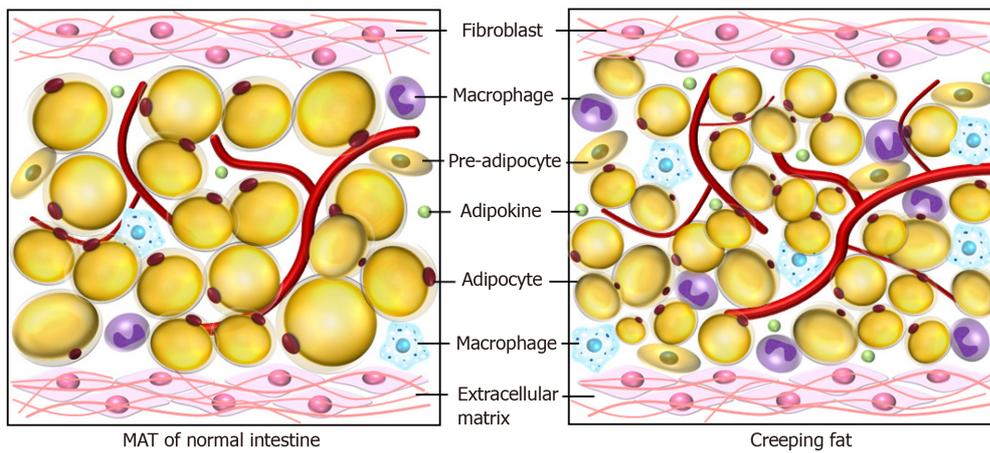


Figure 2 The creeping fat with small-size adipocytes within is a main source of proinflammatory mediators and adipokines. MAT: Mesenteric adipose tissue.

It is revealed the visceral adipose tissue presents a microbiome signature enriched in Proteobacteria of patients with CD[117]. Meanwhile, the abundance of bacteria in visceral adipose tissue can be altered with the clinical status of CD patients. Patients with active CD showed a higher abundance of common mucosal bacteria (*i.e.* Bacteroidetes). Additionally, the formation of creeping fat is associated with translocation of gut bacteria[118]. The creeping fat seems to be a protective response to prevent systemic dissemination of potentially harmful bacterial antigens. The crosstalk between mesentery adipose tissue and microbiota needs further investigation, and the results may provide a new perspective for the management of CD patients.

CROSSLINK BETWEEN MESENTERIC TISSUES

Mesenteric nerves, blood vessels, lymphatics, and adipose tissue are not only associated with intestinal inflammation but also influence other parts of the mesentery [70,119]. The function of mesenteric lymphatics is influenced by endocrine of mesenteric nerves and adipocytes. Nerve fibers around submucosal arteries and mesenteric LVs markedly increase in CD patients, suggesting that neurogenic inflammation is likely associated with early onset lymphatic vascular dilation and submucosa edema. Meanwhile, the structure of the mesenteric LV in hypertrophic mesenteric adipose tissue is mispatterned and ruptured, which can lead to lymph leakage. Leaky lymph factors stimulate adipose tissue to proliferate and effectively elicit an immune response. LVs mediate lipid absorption and transport, share an intimate spatial association with adipose tissue, and regulate the traffic of immune cells[120,121]. Adipokines such as apelin can in turn ameliorate chronic colitis in IL-10^{-/-} mice by promoting intestinal lymphatic function[106]. The neuropeptides, such as vasoactive intestinal peptide, alter lymphatic pumping by decreasing the frequency of lymphatic contractions and hyperpolarizing the lymphatic muscle membrane potential in a concentration-dependent manner[122]. The complex crosstalk between mesenteric nerves, blood vessels, lymphatics, and adipose tissue suggests dysregulation of mesenteric homeostasis in patients with CD. The interaction is likely to play a role in the pathogenesis and disease course of inflammation and remodeling in mesenteric adipose tissue in CD.

CONCLUSION

Accumulating evidence has shown that mesenteric organs including mesenteric nerves, blood vessels, lymphatics, and adipose tissue play a crucial role in the pathogenesis and progress of CD. Existing and emerging clinical evidence strongly suggests that the gut-mesentery axis is bidirectional. The intestinal inflammation and the dysregulation of the crosstalk among mesenteric components interact with each other and contribute to disease aggravation. The mesenteric inflammation may be an independent clinical risk factor associated with surgical outcomes. Recently, Coffey *et*

al[88] reported that inclusion of the mesentery in ileocolic resection for CD is associated with reduced recurrence requiring reoperation, which suggests a more radical resection of mesenteric tissue along with the diseased bowel leads to better surgical outcomes, especially postoperative disease recurrence.

The evaluation of changes in morphology and function of mesenteric nerves, vasculature, lymphatics, and fat mass provide more potential targets for CD treatment. Our group has shown that apelin can ameliorate chronic colitis in Il-10^{-/-} mice by promoting intestinal lymphatic functions[106]. Moreover, a chylomicrons-simulating strategy has been developed, fulfilling sustained drug release in mesenteric lymphatics and enhancing the therapeutic effect on intestinal inflammation by increasing lymphatic drainage[80]. We do believe that more and more agents and strategies targeting mesenteric content will be developed and bring more alternative therapies for CD patients. Mucosal healing has been emphasized as the current dominant standard for disease remission, whereas the changes in morphology and function of mesenteric nerves, vasculature, lymphatics, and adipose tissue can also be monitored during treatment. The improvement or resolution of inflammation of the submucosa, regulation of angiogenesis, enhancement of lymphatic drainage, and amelioration of adipose tissue-associated inflammation could be the next therapeutic goals for CD patients.

REFERENCES

- 1 **Torres J**, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2017; **389**: 1741-1755 [PMID: 27914655 DOI: 10.1016/S0140-6736(16)31711-1]
- 2 **Coffey JC**, O'Leary DP. The mesentery: structure, function, and role in disease. *Lancet Gastroenterol Hepatol* 2016; **1**: 238-247 [PMID: 28404096 DOI: 10.1016/S2468-1253(16)30026-7]
- 3 **Coffey JC**, O'leary DP. Defining the mesentery as an organ and what this means for understanding its roles in digestive disorders. *Expert Rev Gastroenterol Hepatol* 2017; **11**: 703-705 [PMID: 28482706 DOI: 10.1080/17474124.2017.1329010]
- 4 **Coffey JC**, Walsh D, Byrnes KG, Hohenberger W, Heald RJ. Mesentery - a 'New' organ. *Emerg Top Life Sci* 2020; **4**: 191-206 [PMID: 32539112 DOI: 10.1042/ETLS20200006]
- 5 **Sheehan AL**, Warren BF, Gear MW, Shepherd NA. Fat-wrapping in Crohn's disease: pathological basis and relevance to surgical practice. *Br J Surg* 1992; **79**: 955-958 [PMID: 1422768 DOI: 10.1002/bjs.1800790934]
- 6 **Borley NR**, Mortensen NJ, Jewell DP, Warren BF. The relationship between inflammatory and serosal connective tissue changes in ileal Crohn's disease: evidence for a possible causative link. *J Pathol* 2000; **190**: 196-202 [PMID: 10657019 DOI: 10.1002/(sici)1096-9896(200002)190:2<196::Aid-path513>3.0.Co;2-5]
- 7 **Herlinger H**, Furth EE, Rubesin SE. Fibrofatty proliferation of the mesentery in Crohn disease. *Abdom Imaging* 1998; **23**: 446-448 [PMID: 9663285 DOI: 10.1007/s002619900377]
- 8 **CROHN BB**, GINZBURG L, OPPENHEIMER GD. Regional ileitis; a pathologic and clinical entity. *Am J Med* 1952; **13**: 583-590 [PMID: 12996536 DOI: 10.1016/0002-9343(52)90025-9]
- 9 **Batra A**, Heimesaat MM, Bereswill S, Fischer A, Glauben R, Kunkel D, Scheffold A, Erben U, Kühl A, Loddenkemper C, Lehr HA, Schumann M, Schulzke JD, Zeitz M, Siegmund B. Mesenteric fat - control site for bacterial translocation in colitis? *Mucosal Immunol* 2012; **5**: 580-591 [PMID: 22569302 DOI: 10.1038/mi.2012.33]
- 10 **Kredel L**, Batra A, Siegmund B. Role of fat and adipokines in intestinal inflammation. *Curr Opin Gastroenterol* 2014; **30**: 559-565 [PMID: 25188546 DOI: 10.1097/MOG.0000000000000116]
- 11 **Barbier M**, Vidal H, Desreumaux P, Dubuquoy L, Bourreille A, Colombel JF, Cherbut C, Galmiche JP. Overexpression of leptin mRNA in mesenteric adipose tissue in inflammatory bowel diseases. *Gastroenterol Clin Biol* 2003; **27**: 987-991 [PMID: 14732844]
- 12 **Villanacci V**, Bassotti G, Nascimbeni R, Antonelli E, Cadei M, Fisogni S, Salerni B, Geboes K. Enteric nervous system abnormalities in inflammatory bowel diseases. *Neurogastroenterol Motil* 2008; **20**: 1009-1016 [PMID: 18492026 DOI: 10.1111/j.1365-2982.2008.01146.x]
- 13 **Cryan JF**, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, Codagnone MG, Cussotto S, Fulling C, Golubeva AV, Guzzetta KE, Jaggar M, Long-Smith CM, Lyte JM, Martin JA, Molinero-Perez A, Moloney G, Morelli E, Morillas E, O'Connor R, Cruz-Pereira JS, Peterson VL, Rea K, Ritz NL, Sherwin E, Spichak S, Teichman EM, van de Wouw M, Ventura-Silva AP, Wallace-Fitzsimons SE, Hyland N, Clarke G, Dinan TG. The Microbiota-Gut-Brain Axis. *Physiol Rev* 2019; **99**: 1877-2013 [PMID: 31460832 DOI: 10.1152/physrev.00018.2018]
- 14 **Prechtel JC**, Powley TL. The fiber composition of the abdominal vagus of the rat. *Anat Embryol (Berl)* 1990; **181**: 101-115 [PMID: 2327594 DOI: 10.1007/bf00198950]
- 15 **Powley TL**, Phillips RJ. Musings on the wanderer: what's new in our understanding of vago-vagal reflexes? *Am J Physiol Gastrointest Liver Physiol* 2002; **283**: G1217-G1225 [PMID: 12388183 DOI: 10.1152/ajpgi.00249.2002]
- 16 **Chiocchetti R**, Mazzuoli G, Albanese V, Mazzoni M, Clavenzani P, Lalatta-Costerbosa G, Lucchi

- ML, Di Guardo G, Marruchella G, Furness JB. Anatomical evidence for ileal Peyer's patches innervation by enteric nervous system: a potential route for prion neuroinvasion? *Cell Tissue Res* 2008; **332**: 185-194 [PMID: 18317812 DOI: 10.1007/s00441-008-0583-y]
- 17 **Kulkarni-Narla A**, Beitz AJ, Brown DR. Catecholaminergic, cholinergic and peptidergic innervation of gut-associated lymphoid tissue in porcine jejunum and ileum. *Cell Tissue Res* 1999; **298**: 275-286 [PMID: 10571116 DOI: 10.1007/s004419900096]
- 18 **Brinkman DJ**, Ten Hove AS, Vervoordeldonk MJ, Luyer MD, de Jonge WJ. Neuroimmune Interactions in the Gut and Their Significance for Intestinal Immunity. *Cells* 2019; **8** [PMID: 31269754 DOI: 10.3390/cells8070670]
- 19 **Linden DR**. Enhanced excitability of guinea pig inferior mesenteric ganglion neurons during and following recovery from chemical colitis. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G1067-G1075 [PMID: 22961805 DOI: 10.1152/ajpgi.00226.2012]
- 20 **Di Giovangiulo M**, Bosmans G, Meroni E, Stakenborg N, Florens M, Farro G, Gomez-Pinilla PJ, Matteoli G, Boeckxstaens GE. Vagotomy affects the development of oral tolerance and increases susceptibility to develop colitis independently of the alpha-7 nicotinic receptor. *Mol Med* 2016; **22**: 464-476 [PMID: 27341335 DOI: 10.2119/molmed.2016.00062]
- 21 **Wazea SA**, Wadie W, Bahgat AK, El-Abhar HS. Galantamine anti-colitic effect: Role of alpha-7 nicotinic acetylcholine receptor in modulating Jak/STAT3, NF- κ B/HMGB1/RAGE and p-AKT/Bcl-2 pathways. *Sci Rep* 2018; **8**: 5110 [PMID: 29572553 DOI: 10.1038/s41598-018-23359-6]
- 22 **Seyedabadi M**, Rahimian R, Ghia JE. The role of alpha7 nicotinic acetylcholine receptors in inflammatory bowel disease: involvement of different cellular pathways. *Expert Opin Ther Targets* 2018; **22**: 161-176 [PMID: 29298542 DOI: 10.1080/14728222.2018.1420166]
- 23 **Olivier BJ**, Cailotto C, van der Vliet J, Knippenberg M, Greuter MJ, Hilbers FW, Konijn T, Te Velde AA, Nolte MA, Boeckxstaens GE, de Jonge WJ, Mebius RE. Vagal innervation is required for the formation of tertiary lymphoid tissue in colitis. *Eur J Immunol* 2016; **46**: 2467-2480 [PMID: 27457277 DOI: 10.1002/eji.201646370]
- 24 **Willemze RA**, Welting O, van Hamersveld HP, Meijer SL, Folgering JHA, Darwinkel H, Witherington J, Sridhar A, Vervoordeldonk MJ, Seppen J, de Jonge WJ. Neuronal control of experimental colitis occurs via sympathetic intestinal innervation. *Neurogastroenterol Motil* 2018; **30** [PMID: 28745812 DOI: 10.1111/nmo.13163]
- 25 **Willemze RA**, Welting O, van Hamersveld P, Verseijden C, Nijhuis LE, Hilbers FW, Meijer SL, Heesters BA, Folgering JHA, Darwinkel H, Blancou P, Vervoordeldonk MJ, Seppen J, Heinsbroek SEM, de Jonge WJ. Loss of intestinal sympathetic innervation elicits an innate immune driven colitis. *Mol Med* 2019; **25**: 1 [PMID: 30616543 DOI: 10.1186/s10020-018-0068-8]
- 26 **Ağaç D**, Estrada LD, Maples R, Hooper LV, Farrar JD. The β 2-adrenergic receptor controls inflammation by driving rapid IL-10 secretion. *Brain Behav Immun* 2018; **74**: 176-185 [PMID: 30195028 DOI: 10.1016/j.bbi.2018.09.004]
- 27 **Fournier A**, Mondillon L, Luminet O, Canini F, Mathieu N, Gauchez AS, Dantzer C, Bonaz B, Pellissier S. Interoceptive Abilities in Inflammatory Bowel Diseases and Irritable Bowel Syndrome. *Front Psychiatry* 2020; **11**: 229 [PMID: 32300314 DOI: 10.3389/fpsy.2020.00229]
- 28 **Bernstein CN**. The Brain-Gut Axis and Stress in Inflammatory Bowel Disease. *Gastroenterol Clin North Am* 2017; **46**: 839-846 [PMID: 29173525 DOI: 10.1016/j.gtc.2017.08.006]
- 29 **Pellissier S**, Dantzer C, Mondillon L, Trocme C, Gauchez AS, Ducros V, Mathieu N, Toussaint B, Fournier A, Canini F, Bonaz B. Relationship between vagal tone, cortisol, TNF-alpha, epinephrine and negative affects in Crohn's disease and irritable bowel syndrome. *PLoS One* 2014; **9**: e105328 [PMID: 25207649 DOI: 10.1371/journal.pone.0105328]
- 30 **Liu B**, Wanders A, Wirdefeldt K, Sjölander A, Sachs MC, Eberhardson M, Ye W, Ekblom A, Olén O, Ludvigsson JF. Vagotomy and subsequent risk of inflammatory bowel disease: a nationwide register-based matched cohort study. *Aliment Pharmacol Ther* 2020; **51**: 1022-1030 [PMID: 32319125 DOI: 10.1111/apt.15715]
- 31 **Magro F**, Vieira-Coelho MA, Fraga S, Serrão MP, Veloso FT, Ribeiro T, Soares-da-Silva P. Impaired synthesis or cellular storage of norepinephrine, dopamine, and 5-hydroxytryptamine in human inflammatory bowel disease. *Dig Dis Sci* 2002; **47**: 216-224 [PMID: 11837726 DOI: 10.1023/a:1013256629600]
- 32 **Kyösola K**, Penttilä O, Salaspuro M. Rectal mucosal adrenergic innervation and enterochromaffin cells in ulcerative colitis and irritable colon. *Scand J Gastroenterol* 1977; **12**: 363-367 [PMID: 867000 DOI: 10.3109/00365527709180942]
- 33 **Bonaz B**, Sinniger V, Hoffmann D, Clarençon D, Mathieu N, Dantzer C, Vercueil L, Picq C, Trocmé C, Faure P, Cracowski JL, Pellissier S. Chronic vagus nerve stimulation in Crohn's disease: a 6-month follow-up pilot study. *Neurogastroenterol Motil* 2016; **28**: 948-953 [PMID: 26920654 DOI: 10.1111/nmo.12792]
- 34 **Wakefield AJ**, Sawyerr AM, Dhillon AP, Pittilo RM, Rowles PM, Lewis AA, Pounder RE. Pathogenesis of Crohn's disease: multifocal gastrointestinal infarction. *Lancet* 1989; **2**: 1057-1062 [PMID: 2572794 DOI: 10.1016/s0140-6736(89)91078-7]
- 35 **Wakefield AJ**, Pittilo RM, Sim R, Cosby SL, Stephenson JR, Dhillon AP, Pounder RE. Evidence of persistent measles virus infection in Crohn's disease. *J Med Virol* 1993; **39**: 345-353 [PMID: 8492105 DOI: 10.1002/jmv.1890390415]
- 36 **Ludwig D**, Wiener S, Brüning A, Schwarting K, Jantschek G, Stange EF. Mesenteric blood flow is related to disease activity and risk of relapse in Crohn's disease: a prospective follow-up study. *Am J*

- Gastroenterol* 1999; **94**: 2942-2950 [PMID: [10520849](#) DOI: [10.1111/j.1572-0241.1999.01442.x](#)]
- 37 **McLaren WJ**, Anikijenko P, Thomas SG, Delaney PM, King RG. In vivo detection of morphological and microvascular changes of the colon in association with colitis using fiberoptic confocal imaging (FOCI). *Dig Dis Sci* 2002; **47**: 2424-2433 [PMID: [12452374](#) DOI: [10.1023/a:1020631220599](#)]
- 38 **Sakurai T**, Katsuno T, Saito K, Yoshihama S, Nakagawa T, Koseki H, Taida T, Ishigami H, Okimoto KI, Maruoka D, Matsumura T, Arai M, Yokosuka O. Mesenteric findings of CT enterography are well correlated with the endoscopic severity of Crohn's disease. *Eur J Radiol* 2017; **89**: 242-248 [PMID: [28188060](#) DOI: [10.1016/j.ejrad.2016.10.022](#)]
- 39 **Andrade TG**, Fogaça HS, Elia CC, Pitrowsky MT, Souza HS. Crohn's disease activity assessed by Doppler sonography: the role of aortic flow parameters. *Clinics (Sao Paulo)* 2013; **68**: 457-462 [PMID: [23778348](#) DOI: [10.6061/clinics/2013\(04\)04](#)]
- 40 **van Oostayen JA**, Wasser MN, van Hogezaand RA, Griffioen G, Biemond I, Lamers CB, de Roos A. Doppler sonography evaluation of superior mesenteric artery flow to assess Crohn's disease activity: correlation with clinical evaluation, Crohn's disease activity index, and alpha 1-antitrypsin clearance in feces. *AJR Am J Roentgenol* 1997; **168**: 429-433 [PMID: [9016220](#) DOI: [10.2214/ajr.168.2.9016220](#)]
- 41 **van Oostayen JA**, Wasser MN, Griffioen G, van Hogezaand RA, Lamers CB, de Roos A. Diagnosis of Crohn's ileitis and monitoring of disease activity: value of Doppler ultrasound of superior mesenteric artery flow. *Am J Gastroenterol* 1998; **93**: 88-91 [PMID: [9448182](#) DOI: [10.1111/j.1572-0241.1998.088_c.x](#)]
- 42 **Bolondi L**, Gaiani S, Brignola C, Campieri M, Rigamonti A, Zironi G, Gionchetti P, Belloli C, Miglioli M, Barbara L. Changes in splanchnic hemodynamics in inflammatory bowel disease. Non-invasive assessment by Doppler ultrasound flowmetry. *Scand J Gastroenterol* 1992; **27**: 501-507 [PMID: [1631496](#) DOI: [10.3109/00365529209000112](#)]
- 43 **Kircher PR**, Spaulding KA, Vaden S, Lang J, Doherr M, Gaschen L. Doppler ultrasonographic evaluation of gastrointestinal hemodynamics in food hypersensitivities: a canine model. *J Vet Intern Med* 2004; **18**: 605-611 [PMID: [15515573](#) DOI: [10.1892/0891-6640\(2004\)18<605:dueogh>2.0.co;2](#)]
- 44 **Majno G**. Chronic inflammation: links with angiogenesis and wound healing. *Am J Pathol* 1998; **153**: 1035-1039 [PMID: [9777935](#) DOI: [10.1016/s0002-9440\(10\)65648-9](#)]
- 45 **Carmeliet P**. Mechanisms of angiogenesis and arteriogenesis. *Nat Med* 2000; **6**: 389-395 [PMID: [10742145](#) DOI: [10.1038/74651](#)]
- 46 **Bagli E**, Xagorari A, Papetropoulos A, Murphy C, Fotsis T. Angiogenesis in inflammation. *Autoimmun Rev* 2004; **3** Suppl 1: S26 [PMID: [15309776](#)]
- 47 **Firestein GS**. Starving the synovium: angiogenesis and inflammation in rheumatoid arthritis. *J Clin Invest* 1999; **103**: 3-4 [PMID: [9884327](#) DOI: [10.1172/JCI5929](#)]
- 48 **Szekanecz Z**, Koch AE. Vascular endothelium and immune responses: implications for inflammation and angiogenesis. *Rheum Dis Clin North Am* 2004; **30**: 97-114 [PMID: [15061570](#) DOI: [10.1016/s0889-857x\(03\)00116-9](#)]
- 49 **Synnestvedt K**, Furuta GT, Comerford KM, Louis N, Karhausen J, Eltzschig HK, Hansen KR, Thompson LF, Colgan SP. Ecto-5'-nucleotidase (CD73) regulation by hypoxia-inducible factor-1 mediates permeability changes in intestinal epithelia. *J Clin Invest* 2002; **110**: 993-1002 [PMID: [12370277](#) DOI: [10.1172/jci15337](#)]
- 50 **Glover LE**, Colgan SP. Hypoxia and metabolic factors that influence inflammatory bowel disease pathogenesis. *Gastroenterology* 2011; **140**: 1748-1755 [PMID: [21530741](#) DOI: [10.1053/j.gastro.2011.01.056](#)]
- 51 **Kanazawa S**, Tsunoda T, Onuma E, Majima T, Kagiyama M, Kikuchi K. VEGF, basic-FGF, and TGF-beta in Crohn's disease and ulcerative colitis: a novel mechanism of chronic intestinal inflammation. *Am J Gastroenterol* 2001; **96**: 822-828 [PMID: [11280558](#) DOI: [10.1111/j.1572-0241.2001.03527.x](#)]
- 52 **Kapsoritakis A**, Sfiridaki A, Maltezos E, Simopoulos K, Giatromanolaki A, Sivridis E, Koukourakis MI. Vascular endothelial growth factor in inflammatory bowel disease. *Int J Colorectal Dis* 2003; **18**: 418-422 [PMID: [12761641](#) DOI: [10.1007/s00384-003-0495-y](#)]
- 53 **Griga T**, Gutzeit A, Sommerkamp C, May B. Increased production of vascular endothelial growth factor by peripheral blood mononuclear cells in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 1999; **11**: 175-179 [PMID: [10102229](#) DOI: [10.1097/00042737-199902000-00019](#)]
- 54 **Chidlow JH Jr**, Langston W, Greer JJ, Ostanin D, Abdelbaqi M, Houghton J, Senthilkumar A, Shukla D, Mazar AP, Grisham MB, Keivil CG. Differential angiogenic regulation of experimental colitis. *Am J Pathol* 2006; **169**: 2014-2030 [PMID: [17148665](#) DOI: [10.2353/ajpath.2006.051021](#)]
- 55 **Algaba A**, Linares PM, Encarnación Fernández-Contreras M, Figuerola A, Calvet X, Guerra I, de Pousa I, Chaparro M, Gisbert JP, Bermejo F. The effects of infliximab or adalimumab on vascular endothelial growth factor and angiopoietin 1 angiogenic factor levels in inflammatory bowel disease: serial observations in 37 patients. *Inflamm Bowel Dis* 2014; **20**: 695-702 [PMID: [24562175](#) DOI: [10.1097/MIB.0000000000000004](#)]
- 56 **Rudolph EH**, Woods JM. Chemokine expression and regulation of angiogenesis in rheumatoid arthritis. *Curr Pharm Des* 2005; **11**: 613-631 [PMID: [15720278](#) DOI: [10.2174/1381612053381963](#)]
- 57 **Thomas S**, Baumgart DC. Targeting leukocyte migration and adhesion in Crohn's disease and ulcerative colitis. *Inflammopharmacology* 2012; **20**: 1-18 [PMID: [22205271](#) DOI: [10.1007/s12242-012-9381-2](#)]

- 10.1007/s10787-011-0104-6]
- 58 **Lamb CA**, O'Byrne S, Keir ME, Butcher EC. Gut-Selective Integrin-Targeted Therapies for Inflammatory Bowel Disease. *J Crohns Colitis* 2018; **12**: S653-S668 [PMID: 29767705 DOI: 10.1093/ecco-jcc/jjy060]
- 59 **Jackson CS**, Fryer J, Danese S, Vanagunas A, Polensky S, Buchman AL. Mesenteric vascular thromboembolism in inflammatory bowel disease: a single center experience. *J Gastrointest Surg* 2011; **15**: 97-100 [PMID: 20824370 DOI: 10.1007/s11605-010-1336-2]
- 60 **Naik Vietti N**, Vietti Violi N, Schoepfer AM, Fournier N, Guiu B, Bize P, Denys A; Swiss Inflammatory Bowel Disease Cohort Study Group. Prevalence and clinical importance of mesenteric venous thrombosis in the Swiss Inflammatory Bowel Disease Cohort. *AJR Am J Roentgenol* 2014; **203**: 62-69 [PMID: 24951196 DOI: 10.2214/AJR.13.12447]
- 61 **Hatoum OA**, Spinelli KS, Abu-Hajir M, Attila T, Franco J, Otterson MF, Telford GL, Binion DG. Mesenteric venous thrombosis in inflammatory bowel disease. *J Clin Gastroenterol* 2005; **39**: 27-31 [PMID: 15599206]
- 62 **Knod JL**, Crawford K, Dusing M, Collins MH, Chernoguz A, Frischer JS. Angiogenesis and Vascular Endothelial Growth Factor-A Expression Associated with Inflammation in Pediatric Crohn's Disease. *J Gastrointest Surg* 2016; **20**: 624-630 [PMID: 26530519 DOI: 10.1007/s11605-015-3002-1]
- 63 **Danese S**, Sans M, Spencer DM, Beck I, Doñate F, Plunkett ML, de la Motte C, Redline R, Shaw DE, Levine AD, Mazar AP, Fiocchi C. Angiogenesis blockade as a new therapeutic approach to experimental colitis. *Gut* 2007; **56**: 855-862 [PMID: 17170016 DOI: 10.1136/gut.2006.114314]
- 64 **Wu TF**, MacNaughton WK, von der Weid PY. Lymphatic vessel contractile activity and intestinal inflammation. *Mem Inst Oswaldo Cruz* 2005; **100** Suppl 1: 107-110 [PMID: 15962107 DOI: 10.1590/s0074-02762005000900018]
- 65 **Anseline PF**, Wlodarczyk J, Murugasu R. Presence of granulomas is associated with recurrence after surgery for Crohn's disease: experience of a surgical unit. *Br J Surg* 1997; **84**: 78-82 [PMID: 9043461]
- 66 **Li Y**, Ge Y, Gong J, Zhu W, Cao L, Guo Z, Gu L, Li J. Mesenteric Lymphatic Vessel Density Is Associated with Disease Behavior and Postoperative Recurrence in Crohn's Disease. *J Gastrointest Surg* 2018; **22**: 2125-2132 [PMID: 30043133 DOI: 10.1007/s11605-018-3884-9]
- 67 **Dongaonkar RM**, Nguyen TL, Quick CM, Hardy J, Laine GA, Wilson E, Stewart RH. Adaptation of mesenteric lymphatic vessels to prolonged changes in transmural pressure. *Am J Physiol Heart Circ Physiol* 2013; **305**: H203-H210 [PMID: 23666672 DOI: 10.1152/ajpheart.00677.2012]
- 68 **Negrini D**, Moriondo A. Lymphatic anatomy and biomechanics. *J Physiol* 2011; **589**: 2927-2934 [PMID: 21486777 DOI: 10.1113/jphysiol.2011.206672]
- 69 **Liao S**, Cheng G, Conner DA, Huang Y, Kucherlapati RS, Munn LL, Ruddle NH, Jain RK, Fukumura D, Padera TP. Impaired lymphatic contraction associated with immunosuppression. *Proc Natl Acad Sci U S A* 2011; **108**: 18784-18789 [PMID: 22065738 DOI: 10.1073/pnas.1116152108]
- 70 **von der Weid PY**, Rehal S, Ferraz JG. Role of the lymphatic system in the pathogenesis of Crohn's disease. *Curr Opin Gastroenterol* 2011; **27**: 335-341 [PMID: 21543977 DOI: 10.1097/MOG.0b013e3283476e8f]
- 71 **Thaunat O**, Kerjaschki D, Nicoletti A. Is defective lymphatic drainage a trigger for lymphoid neogenesis? *Trends Immunol* 2006; **27**: 441-445 [PMID: 16920402 DOI: 10.1016/j.it.2006.08.003]
- 72 **Von Der Weid PY**, Rehal S. Lymphatic pump function in the inflamed gut. *Ann N Y Acad Sci* 2010; **1207** Suppl 1: E69-E74 [PMID: 20961308 DOI: 10.1111/j.1749-6632.2010.05715.x]
- 73 **Rahier JF**, De Beauce S, Dubuquoy L, Erdual E, Colombel JF, Jouret-Mourin A, Geboes K, Desreumaux P. Increased lymphatic vessel density and lymphangiogenesis in inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **34**: 533-543 [PMID: 21736598 DOI: 10.1111/j.1365-2036.2011.04759.x]
- 74 **Björndahl M**, Cao R, Nissen LJ, Clasper S, Johnson LA, Xue Y, Zhou Z, Jackson D, Hansen AJ, Cao Y. Insulin-like growth factors 1 and 2 induce lymphangiogenesis in vivo. *Proc Natl Acad Sci U S A* 2005; **102**: 15593-15598 [PMID: 16230630 DOI: 10.1073/pnas.0507865102]
- 75 **Cao R**, Björndahl MA, Gallego MI, Chen S, Religa P, Hansen AJ, Cao Y. Hepatocyte growth factor is a lymphangiogenic factor with an indirect mechanism of action. *Blood* 2006; **107**: 3531-3536 [PMID: 16424394 DOI: 10.1182/blood-2005-06-2538]
- 76 **Cao R**, Björndahl MA, Religa P, Clasper S, Garvin S, Galter D, Meister B, Ikomi F, Tritsarlis K, Dissing S, Ohhashi T, Jackson DG, Cao Y. PDGF-BB induces intratumoral lymphangiogenesis and promotes lymphatic metastasis. *Cancer Cell* 2004; **6**: 333-345 [PMID: 15488757 DOI: 10.1016/j.ccr.2004.08.034]
- 77 **Matsuo M**, Yamada S, Koizumi K, Sakurai H, Saiki I. Tumour-derived fibroblast growth factor-2 exerts lymphangiogenic effects through Akt/mTOR/p70S6kinase pathway in rat lymphatic endothelial cells. *Eur J Cancer* 2007; **43**: 1748-1754 [PMID: 17570654 DOI: 10.1016/j.ejca.2007.04.024]
- 78 **Pytowski B**, Goldman J, Persaud K, Wu Y, Witte L, Hicklin DJ, Skobe M, Boardman KC, Swartz MA. Complete and specific inhibition of adult lymphatic regeneration by a novel VEGFR-3 neutralizing antibody. *J Natl Cancer Inst* 2005; **97**: 14-21 [PMID: 15632376 DOI: 10.1093/jnci/dji003]
- 79 **D'Alessio S**, Correale C, Tacconi C, Gandelli A, Pietrogrande G, Vetrano S, Genua M, Arena V, Spinelli A, Peyrin-Biroulet L, Fiocchi C, Danese S. VEGF-C-dependent stimulation of lymphatic

- function ameliorates experimental inflammatory bowel disease. *J Clin Invest* 2014; **124**: 3863-3878 [PMID: 25105363 DOI: 10.1172/JCI172189]
- 80 **Yin Y**, Yang J, Pan Y, Guo Z, Gao Y, Huang L, Zhou D, Ge Y, Guo F, Zhu W, Song Y, Li Y. Chylomicrons-Simulating Sustained Drug Release in Mesenteric Lymphatics for the Treatment of Crohn's-Like Colitis. *J Crohns Colitis* 2021; **15**: 631-646 [PMID: 32978613 DOI: 10.1093/ecco-jcc/jjaa200]
- 81 **Guedj K**, Abitbol Y, Cazals-Hatem D, Morvan M, Maggiori L, Panis Y, Bouhnik Y, Caligiuri G, Corcos O, Nicoletti A. Adipocytes orchestrate the formation of tertiary lymphoid organs in the creeping fat of Crohn's disease affected mesentery. *J Autoimmun* 2019; **103**: 102281 [PMID: 31171476 DOI: 10.1016/j.jaut.2019.05.009]
- 82 **Randolph GJ**, Bala S, Rahier JF, Johnson MW, Wang PL, Nalbantoglu I, Dubuquoy L, Chau A, Pariente B, Kartheuser A, Zinselmeyer BH, Colombel JF. Lymphoid Aggregates Remodel Lymphatic Collecting Vessels that Serve Mesenteric Lymph Nodes in Crohn Disease. *Am J Pathol* 2016; **186**: 3066-3073 [PMID: 27746181 DOI: 10.1016/j.ajpath.2016.07.026]
- 83 **Sura R**, Colombel JF, Van Kruiningen HJ. Lymphatics, tertiary lymphoid organs and the granulomas of Crohn's disease: an immunohistochemical study. *Aliment Pharmacol Ther* 2011; **33**: 930-939 [PMID: 21366631 DOI: 10.1111/j.1365-2036.2011.04605.x]
- 84 **Cao E**, Watt MJ, Nowell CJ, Quach T, Simpson JS, De Melo Ferreira V, Agarwal S, Chu H, Srivastava A, Anderson D, Gracia G, Lam A, Segal G, Hong J, Hu L, Phang KL, Escott ABJ, Windsor JA, Phillips ARJ, Creek DJ, Harvey NL, Porter CJH, Trevaskis NL. Mesenteric lymphatic dysfunction promotes insulin resistance and represents a potential treatment target in obesity. *Nat Metab* 2021; **3**: 1175-1188 [PMID: 34545251 DOI: 10.1038/s42255-021-00457-w]
- 85 **Rahier JF**, Dubuquoy L, Colombel JF, Jouret-Mourin A, Delos M, Ferrante M, Sokol H, Hertogh GD, Salleron J, Geboes K, Desreumaux P. Decreased lymphatic vessel density is associated with postoperative endoscopic recurrence in Crohn's disease. *Inflamm Bowel Dis* 2013; **19**: 2084-2090 [PMID: 23851640 DOI: 10.1097/MIB.0b013e3182971cec]
- 86 **Johnson CM**, Hartman DJ, Ramos-Rivers C, Rao BB, Bhattacharya A, Regueiro M, Schwartz M, Swoger J, Al Hashash J, Barrie A, Pfanner TP, Dunn M, Koutroubakis IE, Binion DG. Epithelioid Granulomas Associate With Increased Severity and Progression of Crohn's Disease, Based on 6-Year Follow-Up. *Clin Gastroenterol Hepatol* 2018; **16**: 900-907.e1 [PMID: 29277619 DOI: 10.1016/j.cgh.2017.12.034]
- 87 **Li Y**, Stocchi L, Liu X, Rui Y, Liu G, Remzi FH, Shen B. Presence of Granulomas in Mesenteric Lymph Nodes Is Associated with Postoperative Recurrence in Crohn's Disease. *Inflamm Bowel Dis* 2015; **21**: 2613-2618 [PMID: 26218143 DOI: 10.1097/MIB.0000000000000541]
- 88 **Coffey CJ**, Kiernan MG, Sahebally SM, Jarrar A, Burke JP, Kiely PA, Shen B, Waldron D, Peirce C, Moloney M, Skelly M, Tibbitts P, Hidayat H, Faul PN, Healy V, O'Leary PD, Walsh LG, Dockery P, O'Connell RP, Martin ST, Shanahan F, Fiocchi C, Dunne CP. Inclusion of the Mesentery in Ileocolic Resection for Crohn's Disease is Associated With Reduced Surgical Recurrence. *J Crohns Colitis* 2018; **12**: 1139-1150 [PMID: 29309546 DOI: 10.1093/ecco-jcc/jjx187]
- 89 **Althoff P**, Schmiegel W, Lang G, Nicolas V, Brechmann T. Creeping Fat Assessed by Small Bowel MRI Is Linked to Bowel Damage and Abdominal Surgery in Crohn's Disease. *Dig Dis Sci* 2019; **64**: 204-212 [PMID: 30276568 DOI: 10.1007/s10620-018-5303-1]
- 90 **Schäffler A**, Fürst A, Büchler C, Paul G, Rogler G, Schölmerich J, Herfarth H. Secretion of RANTES (CCL5) and interleukin-10 from mesenteric adipose tissue and from creeping fat in Crohn's disease: regulation by steroid treatment. *J Gastroenterol Hepatol* 2006; **21**: 1412-1418 [PMID: 16911685 DOI: 10.1111/j.1440-1746.2006.04300.x]
- 91 **Yamauchi T**, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, Sugiyama T, Miyagishi M, Hara K, Tsunoda M, Murakami K, Ohteki T, Uchida S, Takekawa S, Waki H, Tsuno NH, Shibata Y, Terauchi Y, Froguel P, Tobe K, Koyasu S, Taira K, Kitamura T, Shimizu T, Nagai R, Kadowaki T. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature* 2003; **423**: 762-769 [PMID: 12802337 DOI: 10.1038/nature01705]
- 92 **Choi HM**, Doss HM, Kim KS. Multifaceted Physiological Roles of Adiponectin in Inflammation and Diseases. *Int J Mol Sci* 2020; **21** [PMID: 32059381 DOI: 10.3390/ijms21041219]
- 93 **Shapiro L**, Scherer PE. The crystal structure of a complement-1q family protein suggests an evolutionary link to tumor necrosis factor. *Curr Biol* 1998; **8**: 335-338 [PMID: 9512423 DOI: 10.1016/s0960-9822(98)70133-2]
- 94 **Kern PA**, Di Gregorio GB, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor- α expression. *Diabetes* 2003; **52**: 1779-1785 [PMID: 12829646 DOI: 10.2337/diabetes.52.7.1779]
- 95 **Bilski J**, Mazur-Bialy A, Wojcik D, Surmiak M, Magierowski M, Sliwowski Z, Pajdo R, Kwiecien S, Danielak A, Ptak-Belowska A, Brzozowski T. Role of Obesity, Mesenteric Adipose Tissue, and Adipokines in Inflammatory Bowel Diseases. *Biomolecules* 2019; **9** [PMID: 31779136 DOI: 10.3390/biom9120780]
- 96 **Zhang Y**, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994; **372**: 425-432 [PMID: 7984236 DOI: 10.1038/372425a0]
- 97 **Fazolini NP**, Cruz AL, Werneck MB, Viola JP, Maya-Monteiro CM, Bozza PT. Leptin activation of mTOR pathway in intestinal epithelial cell triggers lipid droplet formation, cytokine production and increased cell proliferation. *Cell Cycle* 2015; **14**: 2667-2676 [PMID: 26017929 DOI: 10.1038/372425a0]

- 10.1080/15384101.2015.1041684]
- 98 **Lord GM**, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature* 1998; **394**: 897-901 [PMID: 9732873 DOI: 10.1038/29795]
- 99 **Siegmund B**. Mesenteric fat in Crohn's disease: the hot spot of inflammation? *Gut* 2012; **61**: 3-5 [PMID: 22068165 DOI: 10.1136/gutjnl-2011-301354]
- 100 **Weidinger C**, Ziegler JF, Letizia M, Schmidt F, Siegmund B. Adipokines and Their Role in Intestinal Inflammation. *Front Immunol* 2018; **9**: 1974 [PMID: 30369924 DOI: 10.3389/fimmu.2018.01974]
- 101 **Singh UP**, Singh NP, Guan H, Busbee B, Price RL, Taub DD, Mishra MK, Fayad R, Nagarkatti M, Nagarkatti PS. Leptin antagonist ameliorates chronic colitis in IL-10^{-/-} mice. *Immunobiology* 2013; **218**: 1439-1451 [PMID: 23726523 DOI: 10.1016/j.imbio.2013.04.020]
- 102 **Ziegler JF**, Böttcher C, Letizia M, Yerinde C, Wu H, Freise I, Rodriguez-Sillke Y, Stoyanova AK, Kreis ME, Asbach P, Kunkel D, Priller J, Anagnostopoulos I, Kühl AA, Miehe K, Stumvoll M, Tran F, Fredrich B, Forster M, Franke A, Bojarski C, Glauben R, Löscher BS, Siegmund B, Weidinger C. Leptin induces TNF α -dependent inflammation in acquired generalized lipodystrophy and combined Crohn's disease. *Nat Commun* 2019; **10**: 5629 [PMID: 31822667 DOI: 10.1038/s41467-019-13559-7]
- 103 **Han S**, Wang G, Qiu S, de la Motte C, Wang HQ, Gomez G, Englander EW, Greeley GH Jr. Increased colonic apelin production in rodents with experimental colitis and in humans with IBD. *Regul Pept* 2007; **142**: 131-137 [PMID: 17391779 DOI: 10.1016/j.regpep.2007.02.002]
- 104 **Sawane M**, Kajiya K, Kidoya H, Takagi M, Muramatsu F, Takakura N. Apelin inhibits diet-induced obesity by enhancing lymphatic and blood vessel integrity. *Diabetes* 2013; **62**: 1970-1980 [PMID: 23378608 DOI: 10.2337/db12-0604]
- 105 **Kim JD**, Kang Y, Kim J, Papangeli I, Kang H, Wu J, Park H, Nadelmann E, Rockson SG, Chun HJ, Jin SW. Essential role of Apelin signaling during lymphatic development in zebrafish. *Arterioscler Thromb Vasc Biol* 2014; **34**: 338-345 [PMID: 24311379 DOI: 10.1161/ATVBAHA.113.302785]
- 106 **Ge Y**, Li Y, Chen Q, Zhu W, Zuo L, Guo Z, Gong J, Cao L, Gu L, Li J. Adipokine apelin ameliorates chronic colitis in IL-10^{-/-} mice by promoting intestinal lymphatic functions. *Biochem Pharmacol* 2018; **148**: 202-212 [PMID: 29309764 DOI: 10.1016/j.bcp.2018.01.011]
- 107 **Kredel LI**, Batra A, Stroth T, Kühl AA, Zeitz M, Erben U, Siegmund B. Adipokines from local fat cells shape the macrophage compartment of the creeping fat in Crohn's disease. *Gut* 2013; **62**: 852-862 [PMID: 22543156 DOI: 10.1136/gutjnl-2011-301424]
- 108 **Vernon MA**, Mylonas KJ, Hughes J. Macrophages and renal fibrosis. *Semin Nephrol* 2010; **30**: 302-317 [PMID: 20620674 DOI: 10.1016/j.semnephrol.2010.03.004]
- 109 **Rieder F**, Doyon G, Ouyang Z, West G, Fiocchi C. Adipocyte and Preadipocyte Derived-Mediators Induce a PRO-Fibrogenic Phenotype in Human Intestinal Mesenchymal Cells -A Novel Link Between Fat and Intestinal Fibrosis. *Gastroenterology* 2014; **146** [DOI: 10.1016/s0016-5085(14)60381-4]
- 110 **Sedman PC**, Macfie J, Sagar P, Mitchell CJ, May J, Mancey-Jones B, Johnstone D. The prevalence of gut translocation in humans. *Gastroenterology* 1994; **107**: 643-649 [PMID: 8076751 DOI: 10.1016/0016-5085(94)90110-4]
- 111 **Lin Y**, Lee H, Berg AH, Lisanti MP, Shapiro L, Scherer PE. The lipopolysaccharide-activated toll-like receptor (TLR)-4 induces synthesis of the closely related receptor TLR-2 in adipocytes. *J Biol Chem* 2000; **275**: 24255-24263 [PMID: 10823826 DOI: 10.1074/jbc.M002137200]
- 112 **Schaeffler A**, Gross P, Buettner R, Bollheimer C, Buechler C, Neumeier M, Kopp A, Schoelmerich J, Falk W. Fatty acid-induced induction of Toll-like receptor-4/nuclear factor-kappaB pathway in adipocytes links nutritional signalling with innate immunity. *Immunology* 2009; **126**: 233-245 [PMID: 18624726 DOI: 10.1111/j.1365-2567.2008.02892.x]
- 113 **Kopp A**, Buechler C, Neumeier M, Weigert J, Aslanidis C, Schölmerich J, Schäffler A. Innate immunity and adipocyte function: ligand-specific activation of multiple Toll-like receptors modulates cytokine, adipokine, and chemokine secretion in adipocytes. *Obesity (Silver Spring)* 2009; **17**: 648-656 [PMID: 19148127 DOI: 10.1038/oby.2008.607]
- 114 **Stroth T**, Batra A, Glauben R, Fedke I, Erben U, Kroesen A, Heimesaat MM, Bereswill S, Girardin S, Zeitz M, Siegmund B. Nucleotide oligomerization domains 1 and 2: regulation of expression and function in preadipocytes. *J Immunol* 2008; **181**: 3620-3627 [PMID: 18714036 DOI: 10.4049/jimmunol.181.5.3620]
- 115 **Zhou YJ**, Zhou H, Li Y, Song YL. NOD1 activation induces innate immune responses and insulin resistance in human adipocytes. *Diabetes Metab* 2012; **38**: 538-543 [PMID: 23182460 DOI: 10.1016/j.diabet.2012.08.001]
- 116 **Charrière G**, Cousin B, Arnaud E, André M, Bacou F, Penicaud L, Casteilla L. Preadipocyte conversion to macrophage. Evidence of plasticity. *J Biol Chem* 2003; **278**: 9850-9855 [PMID: 12519759 DOI: 10.1074/jbc.M210811200]
- 117 **Serena C**, Queipo-Ortuño M, Millan M, Sanchez-Alcoholado L, Caro A, Espina B, Menacho M, Bautista M, Monfort-Ferré D, Terrón-Puig M, Núñez-Roa C, Maymó-Masip E, Rodríguez MM, Tinahones FJ, Espin E, Martí M, Fernández-Veledo S, Vendrell J. Microbial Signature in Adipose Tissue of Crohn's Disease Patients. *J Clin Med* 2020; **9** [PMID: 32751800 DOI: 10.3390/jcm9082448]
- 118 **Ha CWY**, Martin A, Sepich-Poore GD, Shi B, Wang Y, Gouin K, Humphrey G, Sanders K,

- Ratnayake Y, Chan KSL, Hendrick G, Caldera JR, Arias C, Moskowitz JE, Ho Sui SJ, Yang S, Underhill D, Brady MJ, Knott S, Kaihara K, Steinbaugh MJ, Li H, McGovern DPB, Knight R, Fleshner P, Devkota S. Translocation of Viable Gut Microbiota to Mesenteric Adipose Drives Formation of Creeping Fat in Humans. *Cell* 2020; **183**: 666-683.e17 [PMID: 32991841 DOI: 10.1016/j.cell.2020.09.009]
- 119 **Chakraborty S**, Zawieja S, Wang W, Zawieja DC, Muthuchamy M. Lymphatic system: a vital link between metabolic syndrome and inflammation. *Ann N Y Acad Sci* 2010; **1207** Suppl 1: E94-102 [PMID: 20961312 DOI: 10.1111/j.1749-6632.2010.05752.x]
- 120 **Harvey NL**. The link between lymphatic function and adipose biology. *Ann N Y Acad Sci* 2008; **1131**: 82-88 [PMID: 18519961 DOI: 10.1196/annals.1413.007]
- 121 **Alitalo K**. The lymphatic vasculature in disease. *Nat Med* 2011; **17**: 1371-1380 [PMID: 22064427 DOI: 10.1038/nm.2545]
- 122 **von der Weid PY**, Rehal S, Dyrda P, Lee S, Mathias R, Rahman M, Roizes S, Imtiaz MS. Mechanisms of VIP-induced inhibition of the lymphatic vessel pump. *J Physiol* 2012; **590**: 2677-2691 [PMID: 22451438 DOI: 10.1113/jphysiol.2012.230599]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

