The Mesenteric Fat and Intestinal Muscle Interface: Creeping Fat Influencing Stricture Formation in Crohn's Disease

Ren Mao, MD, PhD,[,†,‡] Satya Kurada, MD,[†,‡] Ilyssa O. Gordon, MD,[§] Mark E. Baker, MD,[†,¶] Namita Gandhi, MD,[¶] Christine McDonald, PhD,[‡] J. Calvin Coffey, MD,[‖] and Florian Rieder, MD, PhD[†,‡]*

Adipose tissue is present in close proximity to various organs in the human body. One prominent example is fat contained in the mesentery that is contiguous with all abdominal digestive organs including the intestine. Despite the fact that mesenteric fat-wrapping around the inflamed gut (so called "creeping fat") was described as a characteristic feature of Crohn's disease (CD) in the early 1930s, the functional implications of creeping fat have received only recent attention. As a potent producer of fatty acids, cytokines, growth factors, and adipokines, creeping fat plays an important role in regulation of immunity and inflammation. Increasing evidence points to a link between creeping fat and intestinal inflammation in CD, where histopathologic evaluation shows a significant association between creeping fat and connective tissue changes in the bowel wall, such as muscular hypertrophy, fibrosis, and stricture formation. In addition, emerging mechanistic data indicate a link between creeping fat, muscularis propria hyperplasia, and stricturing disease. Information on fat–mesenchymal interactions in other organs could provide clues to fill the fundamental knowledge gap on the role of distinct components of creeping fat in intestinal fibrosis and stricture formation. Future studies will provide important new information that in turn could lead to novel therapeutic agents aimed at prevention or treatment of CD-associated fibrosis and stricture formation.

Key Words: creeping fat, Crohn's disease, stricture, fibrosis, adipose tissue

INTRODUCTION

In 1932, Crohn and collaborators were the first to describe thickened mesenteric fat adjacent to inflamed intestinal segments in a condition they termed "regional ileitis" and named it "creeping fat."[1] This alteration is unique to Crohn's disease (CD) patients and has since been verified and widely accepted as a hallmark of CD.[2] However, the role of creeping fat in intestinal inflammation and the mechanism of creeping fat formation in CD remain largely unknown. The field of adipose tissue research has recently experienced great interest due to the increasing global burden of metabolic diseases such as obesity and diabetes.[3] Adipose tissue is now regarded as an active endocrine and immune organ, secreting a variety of soluble mediators including adipokines, cytokines, fatty acids, and growth factors.[3] The large amount of innate and adaptive immune cells in fat tissue plays a significant role in influencing the function of fat, as the immune system and cellular metabolism are highly interactive.[4] This may be particularly true at interfaces of different tissue compartments, such as mesenteric or creeping fat and the intestine muscularis propria, given the strong link between creeping fat and muscularis propria hyperplasia and subsequent stricture formation in CD.[5, 6] This is important as stricture formation often leads to surgical intervention either from bowel obstruction or penetrating disease. In this narrative review, we will synthesize the available evidence on fat–muscle interactions in the intestine and other organs. We will also provide a putative molecular framework for these interactions and, in particular, how they may contribute to stricture formation in CD.

SEARCH STRATEGY

All relevant literature from 1960 to March 2018 were searched in EMBASE, MEDLINE (a service of the US National Library of Medicine and the National Institutes of Health), and the Cochrane library, supplemented by manually reviewing the reference list of included studies and relevant review articles. The following search criteria were used (all fields): ("fat" OR "adipocyte" OR "adipose tissue" OR "mesenteric fat" OR "creeping fat" OR "fat wrapping") AND

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From the *Department of Gastroenterology and Hepatology, The First Affiliated Hospital of Sun Yat-sen University, China; †Department of Gastroenterology, Hepatology and Nutrition, Digestive Diseases and Surgery Institute, ‡Department of Inflammation and Immunity, Lerner Research Institute, §Department of Pathology, Robert J. Tomsich Pathology & Laboratory Medicine Institute, and ¶Section of Abdominal Imaging, Imaging Institute, The Cleveland Clinic Foundation, Cleveland, Ohio; ‖Department of Surgery, Graduate Entry Medical School, University Hospital Limerick Group, Centre for Interventions in Infection, Inflammation and Immunity, University of Limerick, Limerick, Ireland

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Address correspondence to: Ren Mao, MD, PhD, The First Affiliated Hospital of Sun Yat-sen University, 58 Zhongshan II Road, Guangzhou, 510080, People's Republic of China (maoren2023@gmail.com).

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("remodeling" OR "fibrosis" OR "matrix" OR "proliferation" OR "stricture" OR "hyperplasia"). References from those articles were examined for additional studies meeting these criteria. R.M., S.K., and F.R. assessed the articles for their relevance to the above topic.

CREEPING FAT AND CROHN'S DISEASE

Accumulating evidence points to a link between alterations in mesenteric fat and intestinal disease, including IBD.[2,7–9] The anatomical relationship between the mesentery and the intestine is important in mediating its function. During embryological development, the intestinal endoderm develops within the mesoderm at the intestinal margin of the mesentery.[10] Although epithelial layers are derived from the endodermal germ layer, the mesenchymal layers of the intestine derive from the mesenteric mesenchyme. This histological relationship is retained into adulthood, when mesenteric and intestinal connective tissue are continuous at the region where the mesentery intersects with the intestine (ie, the mesenteric hilum).[11,12]

Creeping fat is pathognomonic of CD.[7,13] It is an extension of mesenteric fat, beginning at the intestinal hilum (ie, the zone where the mesentery and the intestine intersect) and progressively surrounding the intestinal wall, sometimes covering up to >50% of the bowel's circumference (Fig. 1). Intestinal and mesenteric histopathological abnormalities in CD correlate, suggesting an overlap between disease manifestations in the different layers of the intestine and the fat. This points to a connection in cellular and molecular events that could in turn explain the characteristic transmural nature of CD.[7] There is a topographical coupling of mesenteric, mural, and mucosal abnormalities.[14] At the mesenteric transition zone, the mesentery changes from normal to abnormal, and mural and mucosal changes occur in tandem with mesenteric changes.[14]

The wide variety of cell types in the adipose tissue is crucial in determining the function of fat (including creeping fat). Cell types in adipose tissue consist of adipocytes, endothelial cells, immune cells, fibroblasts, pre-adipocytes, and stem cells. Despite the fact that adipocytes account for >90% of fat pad volume, adipocytes are believed to make up only 20%–40% of the cellular content. In fact, every gram of adipose tissue contains 1–2 million adipocytes but 4–6 million stromal vascular cells.[4] Historically considered an innocent bystander, creeping fat is now known to be an active participant in inflammation and immunity.[15] Essentially all immune and nonimmune cell types are represented in healthy mesenteric fat, and its numbers are increased in IBD.[15] This diverse set of cells is capable of producing mediators, including cytokines, adipokines, fatty acids, and growth factors (Table 1, Fig. 2).

In addition to immune cells, there is growing awareness that adipocytes themselves exert an important effect on neighboring cells and tissues. Examples include hair follicles, cardiomyocytes, skeletal muscle, bone marrow, and the lymphatic system.[3] The cross-talk between adipocytes and their

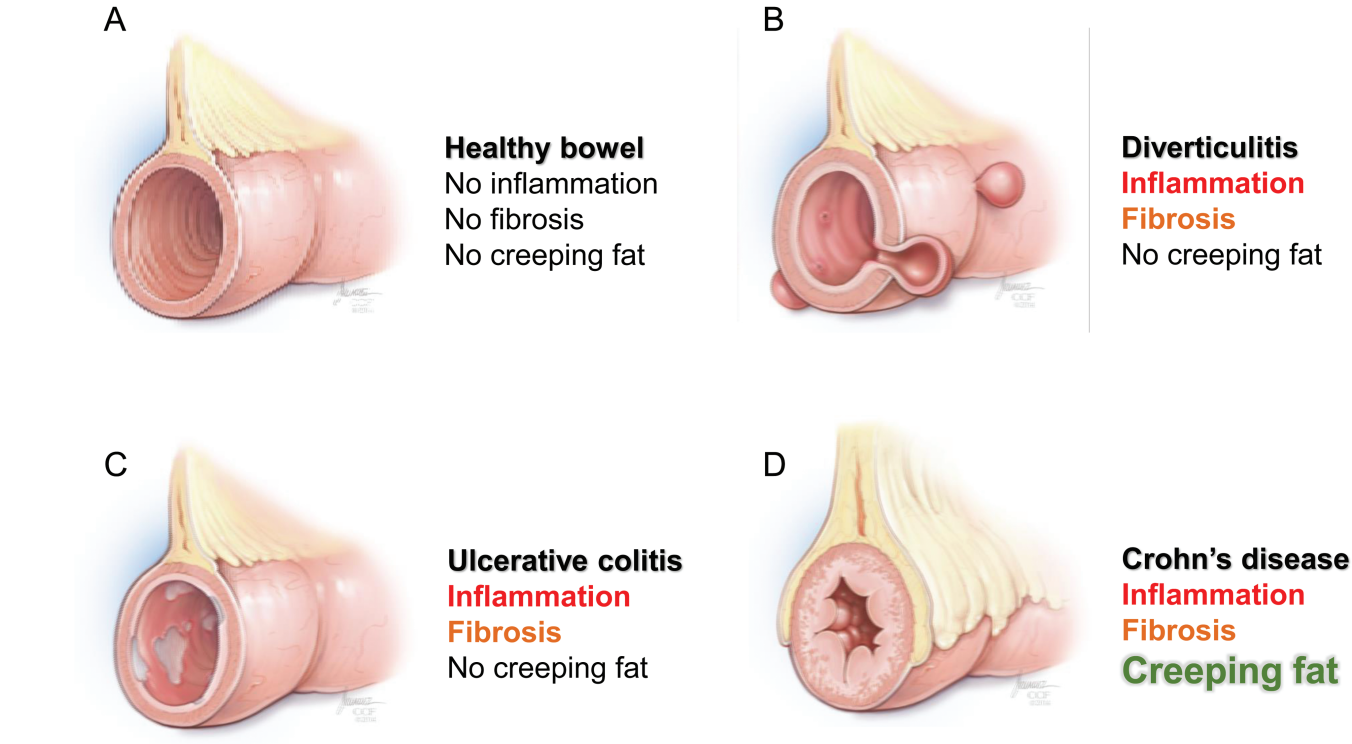

FIGURE 1. Creeping fat is a hallmark of Crohn's disease: (A) healthy bowel, (B) diverticulitis, (C) ulcerative colitis, and (D) Crohn's disease.

TABLE 1. Mediators Derived From Mesenteric Fat In Crohn's Disease

		Reference
Adipokines	Adiponectin	49
	Leptin	50
	Resistin	
	CTRP-3	
Fatty acids	Total, saturated, and polyunsaturated-free fatty acids	21, 51
Cytokines	TNF-α,	16–19, 52
	PPAR-γ	
	M-CSF	
	MCP-1	
	IL-1	
	IL-6	
	IL-10	
	CCL5	
	IL-8	
Growth factors	Ghrelin	18, 49
	VEGF	

Abbreviations: CCL5, chemokine (C-C motif) ligand 5; CTRP-3, C1q/TNF-related protein-3; M-CSF, monocyte colony-stimulating factor; PPAR-γ, peroxisome proliferator-activated receptor γ; VEGF, vascular endothelial growth factor.

environment is mainly mediated in 2 ways: nutritional mechanisms (fatty acids as energy) and via fat-derived autocrine, paracrine, and endocrine molecules.[3] A number of studies indicate a central role of creeping fat in adipose tissue biology by representing a rich source of tumor necrosis factor (TNF), interleukin-6 (IL-6), IL-10, and other pro-inflammatory or profibrotic cytokines (Table 1).[8, 16–19] It has been reported that creeping fat secretes large amounts of adipokines, which are immune modulators in IBD.[20] However, free fatty acid (FFA) secreted by creeping fat and its functional role in neighboring cells and tissues has not been investigated. We recently demonstrated that creeping fat is histologically interpositioned between the serosa and muscularis propria, which suggests that adipocytes in creeping fat are in direct contact with intestinal smooth muscle cells.[21] Moreover, the adipocytes in creeping fat in CD secrete higher amounts of total, saturated, and polyunsaturated FFA compared with mesenteric fat in ulcerative colitis (UC) patients and normal controls, creating a pronounced effect on intestinal smooth muscle cell proliferation.[21]

MESENTERIC FAT AND INTESTINAL FIBROSIS

Intestinal stricture formation is a significant clinical problem in CD. More than half of CD patients develop fibrosis-induced intestinal obstruction, with debilitating symptoms throughout their disease course.[22] Incidence of stricture formation in CD has remained unchanged over the last several decades despite the increasing use of potent biologics and immunosuppressive agents.[23] Currently there are no specific antifibrotic therapies available due to the limited understanding of intestinal fibrogenesis. Similar to fibrosis in other organs, intestinal fibrosis is defined as the combined accumulation of mesenchymal cells and extracellular matrix (ECM) induced by a complex mix of factors including microbial components, environmental factors, immune cells, nonimmune cells, and their products.[24] However, despite sharing common mechanisms, knowledge about the pathogenesis of intestinal fibrosis lags far behind that of organs other than the gut.[25] Early data from macroscopic findings indicate that the presence of creeping fat was associated with muscularis propria hyperplasia and stricturing disease.[5] In a study investigating 20 patients undergoing ileal resection for CD and 20 normal controls, serosal fat-wrapping was present in all cases, and the extent of fat-wrapping correlated closely with the degree of chronic inflammation.[5] In a consecutive and unselected group of 27 intestinal resections performed on 25 patients with histologically confirmed CD, fat-wrapping was identified in 12 of 16 ileal resections and in 7 of 11 large bowel resections. This fat-wrapping correlated with transmural inflammation, and there was a significant relationship between fat-wrapping and other connective tissue changes, including fibrosis, muscular hypertrophy, and stricture formation.[6] These findings suggest that serosal connective tissue changes including fat-wrapping in CD are related to local effects of underlying chronic inflammatory infiltrates including fibrosis.

The role of visceral adipose tissue in fibrosis and remodeling in organs such as the heart, joints, and vessels has recently raised great interest.[26–28] Information from these organs, as described below, may offer important clues to define the impact of mesenteric fat on intestinal fibrosis and the so far elusive pathogenesis of creeping fat formation in CD.

Epicardial Adipose Tissue and Fibrosis

Accumulating evidence points to an association between pericardial fat and occurrence of atrial fibrillation (AF). In AF, atrial myocardial fibrosis appears to be prominent and may lead to functional abnormalities,[29] which makes this observation highly relevant for CD-associated strictures. In the Framingham Heart Study, pericardial fat volume was an independent predictor of AF development even after adjusting other AF risk factors.[30] As occurs in the case of creeping fat in CD, epicardial adipose tissue (EAT) is present between the visceral pericardium and epicardium, in direct contact with the adjacent myocardium.[31] EAT includes periatrial, periventricular, and pericoronary fat. As a result of direct contact, there is no anatomical or histological barrier that may prevent crosstalk between epicardial fat and adjacent muscle.[31] Histological analysis of the human myocardium has identified fibrosis at the interface between adipose and myocardial tissues. Marked interstitial fibrosis of the neighboring myocardium has often been noted in these studies.[31] Pangenomic

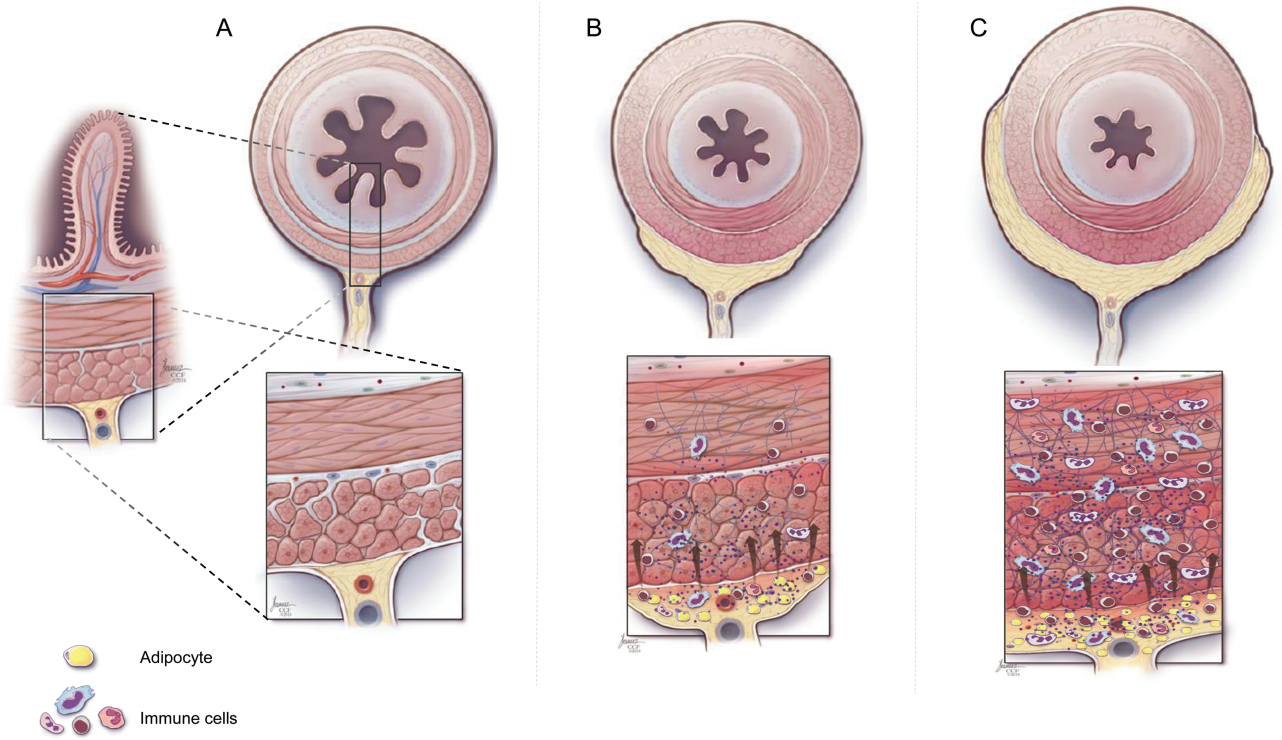

FIGURE 2. Immune cells and nonimmune cells including adipocytes in the mesenteric fat secrete a wide range of mediators, including adipokines (adiponectin, leptin, resistin, and CTRP-3), cytokines (TNF-α, IL-1, IL-6, IL-10, and CCL5), growth factors (VEGF, b-FGF), and free fatty acids (oleic acid, palmitic acid, and stearic acid), which could induce proliferation of intestinal mesenchymal cells (fibroblast, myofibroblast, and smooth muscle cell) and enhance extracellular matrix production. A, Healthy bowel. B and C, Crohn's disease with creeping fat. Abbreviations: b-FGF, vasic fibroblast growth factor; CCL5, chemokine (C-C motif) ligand 5; CTRP-3, C1q/TNF-related protein-3; VEGF, vascular endothelial growth factor.

transcriptomic studies identified a specific transcriptomic signature in human EAT compared with subcutaneous fat (SAT). More than 400 genes are commonly expressed across epicardial fat depots. Among these are genes involved in extracellular matrix remodeling (associated with the collagen IV, VI, thrombospondin 3, laminin alpha 2, fibronectin 1 genes), inflammation, and thrombosis pathways.[32] The secretome of human EAT obtained from patients undergoing coronary bypass surgery, but not from SAT, rapidly leads to increased fibrosis in atrial organo-culture.[31] Among the adipo-fibrokines secreted by EAT, activin A (a member of the TGF-β superfamily) may be an important mediator of this pro-fibrotic effect. Indeed, activin A enhanced fibrotic events, such as liver fibrosis and cardiac fibrosis, whereas anti-activin A antibody prevented such events.[33–35]

The adipocyte-derived hormone leptin may induce cardiac fibrosis by promoting endothelial dysfunction, m-TOR pathway activation, and oxidative stress.[26, 36] A recent interesting study demonstrated that visceral adipose tissue contributes to age-related cardiac fibrosis and dysfunction through modulation of fibroblast senescence by osteopontin production.[37] Modulation of the secretome from visceral adipose tissue might be a potential therapeutic strategy for cardiac fibrosis and remodeling.[37] Taken together, this evidence suggests that mediators secreted from epicardial adipose tissue contribute to cardiac fibrosis.

Infrapatellar Fat Pad and Osteoarthritis

The effects of periarticular adipose tissue on nearby joint disease such as osteoarthritis (OA) have also come under the spotlight in recent years. Eymard et al.[38] showed that intra-articular adipose tissue (IAAT) has a distinct histological phenotype compared with subcutaneous adipose tissue. Fibrosis and vascularity are increased in all IAAT compared with SAT. IAAT adipocytes are smaller in size compared with their subcutaneous counterparts. Differential expression of genes involved in developmental signaling, lipid handling, and general metabolism is apparent when IAAT and SAT are compared. IAAT secretes more IL-6, IL-8, and prostaglandin E2 compared with SAT. Barboza et al.[27] identified prominent fibrosis in the infrapatellar fat pad (IFP), which is the main IAAT of the knee. Mice fed a high-fat diet for 20 weeks develop osteophytes and early structural changes in cartilage. Obesity-associated changes in IFP tissue are associated with increased expression of genes associated with fibrosis and ECM production.[27] This information suggests that IAAT may play a deleterious role in OA by affecting joint homeostasis

with its pro-inflammatory and pro-fibrotic phenotype and close interaction with synovium.

Perivascular Fat and Atherosclerosis

Perivascular fat (PVAT) is directly contiguous with the vascular adventitia. It has been suggested that PVAT may exert pathogenic effects in atherosclerosis development and that this is facilitated by contiguity between PVAT and blood vessels.[28] PVAT plays an important role in local vascular homeostasis. Factors including adiponectin, leptin, and monocyte chemoattractant protein-1 (MCP-1) released from PVAT may contribute to inflammation and smooth muscle proliferation and promote atherosclerotic or neointimal growth.[39] Findings in rodent models show that aging and diet-induced obesity enhance the ability of PVAT to stimulate proliferation of human smooth muscle cells by releasing hydrosoluble protein growth factors.[40] Collectively, these data indicate that perivascular adipose tissue could play a pathobiological role in cardiovascular diseases such as atherosclerosis.

Creeping Fat and Intestinal Fibrosis

The composition of activated adipose tissue, with adipocytes secreting a broad spectrum of fatty acids, adipokines, and cytokines adjacent to adipose tissue–derived stromal cells and immune effector cells in creeping fat, creates a complex network of processes shaping local immune responses in the adjacent inflamed intestinal wall. It is reported that the adipocyte-dependent microenvironment within the creeping fat of patients with CD promotes an M2 macrophage subtype, which exerts an important pro-fibrotic role through the secretion of large amounts of pro-fibrotic factors such as TGF-β.[41, 42]

Our preliminary observations indicate that creeping fat–derived mediators such as FFAs, but not adipokines, induce a differential and selective proliferative response by human intestinal fibroblast (HIF) and human intestinal muscle cells (HIMCs). This response is lacking in matrix secretion, IL-6 production, α-SMA expression, and cell migration.[43] Interestingly, creeping fat secreted higher amounts of total, saturated, and polyunsaturated FFA compared with mesenteric fat in UC patients and normal controls. FFA increased HIMC and HIF proliferation, but not proliferation of intestinal epithelial or endothelial cells, pre-adipocytes, or adipocytes, which suggests that the FFA-induced proliferation effect is intestinal mesenchymal cell specific. Exposure of HIMC to whole creeping fat tissue and fat-conditioned medium dramatically upregulated HIMC proliferation compared with UC and normal mesenteric fat. Long-chain FFA-induced HIMC proliferation was dependent on the kinases p38MAPK, PKC, and PI3K, but not classical pathways involved in FFA uptake, such as MyD88, TLR2, TLR4, NF-kB, or CD36.[21, 43] Inhibiting Acyl-CoA synthetase and sphingosine biosynthesis reduced the palmitate-induced HIMC proliferation.[21] These data suggest a novel role of creeping fat on HIMC hyperplasia, which is a major contributor to intestinal stricture formation in CD.

CREEPING FAT, MESENTERIC FAT, AND CD: IMAGING

In the past, CD was primarily imaged with the standard, barium-based small bowel series. Proliferation of mesenteric fat was only inferred on this examination by bowel loop separation. With the advent of cross-sectional imaging, primarily computed tomography (CT) and magnetic resonance (MR) imaging, mesenteric fat is directly identified as a below-water attenuation (generally <70–80 Hounsfield Units) process between the bowel loops. The literature would suggest that any proliferation of this fat is "creeping fat."[44]

However, we know of no investigation that identifies the fat proliferation identified on imaging as indicative of pathologic fat-wrapping or creeping fat. This fatty proliferation may in fact correlate with fat-wrapping or represent exuberant fat-wrapping, but we do not know this. Thus, it is best to use the term fibrofatty proliferation when identified on imaging.[45]

To date, we have no method of identifying on imaging what pathologists and surgeons identify as fat-wrapping or creeping fat. Further, although imaging can identify changes in perienteric fat, such as soft tissue stranding or edema, in general the mesenteric fat attenuation on CT or signal on MR is fairly uniform visually. Even when the perienteric fat adjacent to abnormal bowel is visually compared with perienteric fat adjacent to normal bowel, radiologists are unable to find substantial differences. We believe that computer-based radiomics or artificial intelligence methods of perienteric fat evaluation, especially on MR, may give us insight into the processes occurring in fat that are visually obscure.

FUTURE OUTLOOK

Fat–mesenchymal cell interactions appear to be important in tissue remodeling in multiple organs, including the intestine. Future studies should focus on specific features of CD that are strongly associated with changes in the mesentery: creeping fat, axial polarity, transmural inflammation, and mesenteric shortening.[46] Special emphasis should be put on fat–mesenchymal interactions at the zone of intersection between the mesentery and the intestine. Although this region is a least 2 meters in length, it is remarkably understudied in general.[47, 48]

Currently, there are no animal models that reproduce the mesenteric phenomena observed in CD (ie, fat-wrapping, mesenteric thickening and fibrosis, and the mesenteric transition zone). Novel animal models that reproduce mesenteric manifestations of CD with a high level of fidelity are needed to elucidate mechanisms of creeping fat formation or fat–mesenchymal interactions in vivo. Alternatively, complex ex vivo 3D culture models may enable the mechanistic investigation of this biologically relevant phenomenon.

The ultimate goal remains the development of novel targets for the treatment of CD-associated strictures and the avoidance of radical surgery. This will require pharmacotherapeutic manipulation of fat–mesenchymal cellular interactions.

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