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Adipose Tissue and IBD Pathogenesis

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Abstract

Creeping fat has long been recognized as an indicator of Crohn's disease activity. Although most patients with Crohn's Disease (CD) have normal or low BMI, the ratio of intra-abdominal fat to total abdominal fat is far greater than that of controls. The obesity epidemic has instructed us on the inflammatory nature of hypertrophic adipose tissue and similarities between mesenteric depots in obese and CD patients can be drawn. However, several important physiological differences exist between these two depots as well. While the molecular basis of the cross-talk between mesenteric adipose and the inflamed intestine in CD is largely unknown, novel evidence implicate neuropeptides along with adipocyte-derived paracrine mediators (adipokines) as potential targets for future investigations and highlight adipose tissue physiology as a potential important determinant in the course of IBD.

Crohn's Disease and Mesenteric Adipose

Long before the concept of adipose tissue as an immune organ began to capture the interest of scientists in the early 1990's, mesenteric fat had been shown to be an important indicator of regional disease activity in CD patients. Fat wrapping or "creeping fat" has been recognized at least since the early 1930's and used by surgeons to help identify the most diseased regions of the bowel [1]. Fat wrapping is defined as fat extending from the mesenteric attachment to partially cover the small or large intestine, resulting in a loss of the bowel-mesentery angle [2] (Figure 1). In general, fat which covers more than 50% of the bowel circumference, is considered to be of significant importance and is a common and specific feature of CD. A retrospective review of 225 small intestinal resections found fat wrapping in more than 53% of CD cases, but not in resections performed for other indications such as intestinal ischemia, Meckel's diverticulum, carcinoma, lymphoma, peforation from various etiologies, or radiation enteritis [3]. Fat wrapping is positively correlated with muscular hypertrophy, fibrosis, transmural inflammation, and stricture formation at the gross level, and macrophage and lymphocyte pervascular infiltration on histology[3] .

Increased body mass index (BMI) predicts poorer outcome and earlier time to first surgery in patients with CD [4]. Obesity is associated with the development of more active IBD and requirement for hospitalization, and decreases in the time span between diagnosis and surgery [5]. This may come as a surprise given the importance of malnutrition in CD patients.

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Although most patients with CD are underweight, the ratio of intraabdominal fat to total abdominal fat is far greater than in controls when assessed by MRI in these patients [6]. In this study fat accumulation in the mesentery of patients with CD is an early event and does not correlate with duration or intensity of disease, raising the question of whether it could be related to IBD pathogenesis.

Adipose Tissue and the Inflammatory Features of Obesity

The importance of adipose tissue in disease pathogenesis has become better appreciated as the prevalence of obesity has reached epidemic proportions. Obesity has now overcome smoking as the leading cause of morbidity and mortality in the US [7], which if left unchecked is predicted to lead to a regression in life expectancy in the US in the 21st century [8]. Interest into the mechanisms behind the enormous contribution of obesity to the US disease burden has led to discoveries that suggest that obesity represents a state of low grade inflammation. Adipocytes function much like macrophages, surveying their environment for microbial products [9], and mediating innate immune responses [10], while preadipocytes have direct phagocytic function [11].

Mesenteric adipose tissue from obese animals shows significantly higher density of macrophages compared to lean littermates and recruitment of these cells may by due to the release of monocyte chemoattractant protein-1 (MCP-1) from preadipocytes and endothelial cells [12]. In gonadal tissue of immunodeficient mice that received stem cell transplants, macrophages are of bone marrow origin indicating, migration of these cells to this area [13]. However, adipocytes may possess the ability to de-differentiate into preadipocytes [14], which possess several of the features of macrophages, including bacterial phagocytosis [11]. Preadipocytes are also able to rapidly differentiate into macrophages [11]. Thus, the increased number and activity of macrophages in visceral adipose tissue may result not only from macrophage migration but also from local adipocyte plasticity. Indeed, the preadipocyte gene expression profile is closer to macrophages than mature adipocytes [14]. Over 50 adipocyte derived mediators termed adipokines have been identified [15]. Most notable among them are leptin and adiponectin together with other prominent proinflammatory mediators not specific to adipocytes, such as TNFα, IL-6, and IL-8. Leptin is a pro-inflammatory appetite suppressant secreted in quantities proportional to total fat mass that regulate adipocyte and preadipocyte Toll-like receptors expression *in vitro* [16]. Adiponectin is an anti-inflammatory adipokine that seems to play a protective role against the development of metabolic syndrome [17]. Its expression levels and secretion are inversely related to fat mass. An increasing amount of evidence have demonstrated an adiponectin-induced direct inhibition of proinflammatory pathways, including those regulated by TLRs [18, 19], via inhibition of NF-κB, in several cell types including adipocytes [20]. In addition, adiponectin inhibits proinflammatory cytokine secretion while it upregulates secretion of the anti-inflammatory cytokine IL-10 [18, 21], and reduces leptin-mediated TNFα expression via inhibition of MAPK activation [22]. Resistin, another adipokine, increases the expression of TLR-2 and activates JNK1 and 2 in human subcutaneous adipocytes [23]. Interestingly resistin levels are significantly increased during obesity [24].

Much of the morbidity associated with obesity is secondary to the associated metabolic syndrome that includes type 2 diabetes, dyslipidemia, and hypertension [25]. Intra-abdominal obesity is of particular importance since clinically, waist circumference rather than absolute weight or BMI is more closely correlated with the development of metabolic syndrome [2627]. The involvement of intra-abdominal adipose tissue in metabolic syndrome development correlates well with elevations in cytokine levels observed in obese individuals. In particular, IL-6 is 50% higher in the portal vein of obese individuals compared to the radial artery, underlining the importance of mesenteric fat for these systemic elevations [28].

In addition to elevated circulating cytokines in obese individuals, circulating macrophages are also in an activated state characterized by increased NF-κB nuclear translocation and decreased NF-κB inhibitor IκBβ levels [29]. In these individuals the concentration of plasma free fatty acid (FFA) is significantly corelated not only with BMI but also with IL-6 and TNF-α mRNA expression, as well as plasma CRP levels. It is likely that hyperlipidemia induces inflammatory responses via activation of the same signaling pathways as lipopolysacharide [30]. This hypothesis is demonstrated in studies using hyperlipidemic myD88 deficient mice, which have deficient signal transduction downstream of Toll like receptors, where these animals show significant reduction in early atheroscerosis despite the increases in their circulating FFAs.

Adipocyte-specific effects on innate immune responses have been well documented and are shown to be affected by obesity [23, 31]. In adipocytes, TLR-2 expression was upregulated by LPS in a TLR-4-dependent manner [32]. In the same cells, LPS treatment induced IL-6 and TNFa secretion via NF-kB-associated pathways. TLR-2 levels are incresed during obesity and affected by increased resistin levels, the levels of which are also correlated with those of adiposity. Thus, adipocytes demonstrate a strong proinflammatory potential with their ability to induce innate immune responses along with their capacity to produce specific molecules that affect the expression of inflammatory mediators. Interestingly, levels of proinfammatory mediators during obesity are not only affected by the levels of adiposity, but also interact with each other to furhter influence the inflammatory millieu in fat depots in obese states [33, 34].

Adipose Tissue and IBD Pathogenesis

The earliest and most important IBD susceptibility loci have been mapped in nucleaotide-binding oligomerization domains (NOD) now called N-terminal caspase recruitment domain (CARD) [35]. Recent studies employing genome-wide association studies have now strengthened this association identifying novel risk factors as well as protective splice variants linking IBD with these domains [36]. Mutations especially within the NOD2/CARD15 region increase suseptability to CD 20 to 40 fold [37, 38] and predict earlier onset of the disease, ileal location, increased risk for the requirement of resection, and an increased risk of post-operative relapse after resection [39]. Similar to the Toll-like receptors also expressed by adipocytes and preadipocytes [16], NOD/CARD receptors are microbial pattern recognition molecules of the innate immune system that detect bacterial products such as peptidoglycans in the cytoplasm and activate transcription factors and intracellular signaling kinases. NOD/CARD domains code for receptors present on antigen presenting cells such as macrophages and are constitutively expressed by preadipocytes [40]. Intererstingly, NOD1/2$^{-/-}$ deficient mice demonstrate less insulin intolerance and adipose tissue inflammation in response to high fat diet while direct activation of NOD1 in adipocytes is associated with similar metabolic changes [41]. Given the magnitude of these effects and the abundanse of the receptors and their signaling mediators in adipocytes, understanding the mechanism that makes these receptors so relevant to the pathogenesis of IBD is likely to shed light into the role of mesenteric fat in the pathogenesis of these diseases.

A better understanding of the molecular mechanism of the association between the function of the adipose tissue and the development of intestinal inflammatory pathological conditions can be achieved via the investigation of the potential involvement of adipocyte-specific mediators (adipokines) in the generation of these responses. Studies employing IBD models have demonstrated an important proinflammatory role for leptin during colitis [10, 42], while increased leptin expression is found in the colonic lumen of IBD patients compared to controls [9]. In addition, increased levels of the leptin receptor in T lymphocytes are associated with increased severity of colitis in mice [43]. Leptin also regulates CD4+ T-cell

polarization in vitro and in vivo [44]. Together, these results implicate leptin in the development of chronic intestinal inflammation. Interestingly, despite the ability of other cell types to produce and secrete leptin the effects of leptin in colitis are strongly associated with adipocyte-derived leptin [45].

Several studies indicate a potential role for adiponectin in regulating IBD-associated inflammatory responses. Significantly increased levels of adiponectin within the newly developed “hypertrophic” mesenteric fat mass are found during CD [46]. Interestingly, adiponectin expression from hypertrophic adipocytes has been shown to decrease dramatically during obesity, while this is not the case for “hypertrophic” CD-associated fat [47]. In another study, female and male CD patients had lower adiponectin levels compared to UC, and adiponectin was lower in female CD patients compared to female control subjects [48]. Adiponectin was higher in UC with inactive disease, while corticosteroid treatment is associated to elevated adiponectin in male CD patients [48]. Valentini et al showed that, compared to controls, adiponectin levels were decreased in both active and inactive IBD disease [49]. Interestingly, infliximab therapy in IBD patients did not alter levels of leptin or adiponectin, but significantly reduced serum levels of the adipokine resistin [50].

Additional evidence for a potential crosstalk between adipose and intestinal tissue as it relates to the development of intestinal inflammation is provided by calprotectin, a biomarker of intestinal inflammation and increased risk for the development of colorectal cancer, the levels of which also increase significantly with obesity [51]. Intervention to reduce C-reactive protein serum levels, also increased during obesity, is able to correct these changes [52, 53].

Finally, recent studies using the DSS colitis mouse model, demonstrated that adipose tissue-derived stem cells ameliorate the clinical and histopathological severity of colitis, abrogate weight loss, diarrhea and inflammation, and increase survival [54]. This is accomplished, at least in part via the induction of IL-10 secreting T regulatory cells and the impairment of Th1 cell activation. Overall, adipose tissue-derived stem cells decreased inflammatory responses, including the down-regulation of proinflammatory cytokine expression from macrophages.

Mesenteric Adipocytes in CD patients as a Source of Adipokines

TNF-α is a crucial mediator involved in the pathopysiology of IBD, and therapy with anti TNF-α monoclonal antibodies along with corticosteroids, are the only agents shown to induce remission during active CD [55, 56]. As discussed above and as is also the case with obesity, mesenteric adipose tissue in patients with CD is a source of many cytokines in significant concentrations that are released directly adjacent to the bowel and are differentially regulated. Adipose tissue is composed of mature adipocytes, preadipocytes, endothelial cells, fibroblasts, macrophages, and lymphocytes. A study in mouse gonadal adipose tissue showed that macrophages and endothelial cells were responsible for greater production of TNF-α and IL-6 compared to adipocytes [13]. When mesenteric adipose tissue in patients with CD was studied, however, it was found that adipocytes themselves were a major mesenteric source of TNFα [6]. No positive immunohistochemical staining for TNFα was observed in the subcutaneous fat of patients with CD or the mesenteric or subcutaneous fat of healthy controls, however mesenteric adipose from patients with CD did stain positive [6]. In-situ hybridization of a TNF-α antisense probe was used to further localize the source of TNF-α. The probe detected no TNF-α in mesenteric adipose tissue from controls whereas all specimens from CD patients were positive. In addition, only some of the mononuclear cells stained positive while all of the adipocytes were positive with the TNF-α signal present in the cytoplasmic and perinuclear regions [6].

Stool calprotectin is a marker of inflammation of the bowel and levels are increased in obesity. Intervention to reduce serum C-reactive protein (CRP) levels abolishes this association [51], while weight loss also reduces CRP levels [53]. Interestingly, CRP levels are significantly increased in the mesenteric fat depots of CD patients while bacterial products and proinflammatory cytokines are shown to induce CRP mRNA expression in 3T3-L1 preadipocytes [57].

Growth hormone deficiency is associated with increased central adiposity and has been consistently observed in patients with CD [58, 59]. Clinical trials of human growth hormone as a therapy for CD have shown it to be effective for the treatment of clinical disease as well as growth failure [60, 61]. In addition over production of the hormone was shown to be beneficial in animal models of colitis [62]. These results are interesting in that mitigation of the deleterious effect of intra-abdominal fat may explain the therapeutic effect of growth hormone in CD. Further MRI analysis of patients pre and post growth hormone treatment to determine the effect of this agent on mesenteric fat depot size may add information on the potential use of growth hormone as a therapeutic agent.

Neuropeptides are a link between adipose tissue and IBD

The potential involvement of neuropeptides in IBD has been demonstrated by several lines of evidence (reviewed in [63, 64]). Studies from our group have also demonstrated proinflammatory effects of neuropeptides on human adipocytes as well as the presence of the receptors for substance P (SP) and neurotensin (NT) on the surface of these cells [65, 66]. SP and NT treatment of preadipocytes induced the expression of IL-8 and IL-6, respectively in an NF-κB-dependent manner. Interestingly, the levels of these receptors increased in adipose tissue after the induction of experimental colitis in mice. Such proinflammatory effects may create a cycle of events that contributes to inflammatory cell recruitment and activation observed within the “creeping” fat depots of IBD patients, especially via the chemo attraction of neutrophils (potential model reviewed in [64]).

Another potential avenue by which SP may affect the adipose-intestinal interactions during IBD is via direct effects on mesenteric fat depot physiology and the development of “creeping” fat around the inflamed areas of the intestine during CD. It has been suggested that autocrine signals as well as secreted factors acting in a paracrine fashion may affect preadipocyte proliferation and differentiation [67, 68]. SP is present in fat depots [68-70], and is thought to participate in brown adipose tissue trophic responses [71, 72]. In a recent study we have also demonstrated that SP can affect fat depot size via effects on preadipocyte replication and apoptosis. In particular, treatment of preadipocytes with SP increased their proliferative potential while it decreased FasL-induced apoptosis [73]. In the same study, we showed that SP-induced increased proliferation was likely caused via activation of Akt and PKCθ along with the activation of the translational promoters p70 S6 kinase and 4E-BP1. Protection from apoptosis was likely due to induction of PARP and caspase-7 cleavage as well as reduction of caspase-3 activation.

Thus neuropeptides may link adipose and intestinal responses during IBD by either affecting the formation of the “creeping” fat mass (yet of unknown contribution) in CD, or by their capacity to induce proinflammatory responses in adipocytes which may in turn trigger recruitment of immune cells around the area of the inflamed intestine.

Comparing Obesity and CD Mesenteric Fat Depots

Although obesity research has shed light on the role of adipose tissue in the pathogenesis of IBD there are important differences between the mesenteric fat depots in these two disease states. Adipose tissue in obese individuals, whether subcutaneous or mesenteric, grows by

hypertrophy. Increased adipocyte size in obese individuals correlates with overproduction of adipokines [74] and increased macrophage infiltration [75]. In contrast, mesenteric fat accumulation in CD appears to occur as a result of hyperplasia. There are approximately four times as many adipocytes per unit area than adipocytes from controls [76]. While both diseases involve the release of adipokines as part of a chronic inflammatory condition, obese individuals rarely develop symptoms of IBD, and metabolic syndrome is rare in IBD patients, unless related to chronic corticosteroid use. As described above, adiponectin production is decreased during central obesity but increased during IBD[77, 46]. Although serum TNFα appears to be a product of both obese and CD mesenteric fat depots, the cell types producing TNFα in these two disease states may be different. TNFα in obese mesenteric adipose may be released from stromal vascular cells, whereas in CD adipocytes may represent the main source [13, 6]. At this point it is not evident which of these distinctions, if any, can explain the pathophysiologic difference seen between the obesity and CD disease states. Indeed, not yet identified differences in these two “inflammatory” fat depots may account for the disparity of symptomatology between obese and IBD patients.

Hence, it is clear that the term “hypertrophic” is not appropriate when adipocytes and not whole mesenteric adipose tissue are described in the case of CD. Indeed, a recent study [78] has also confirmed that creeping fat adipocytes isolated from CD patients are smaller in size (due to reduced lipid metabolism pathway activation) and not hypertrophic. Thus, changes in fat tissue size and distribution under different pathological conditions should be characterized separately, while adiposity alone should not be the sole criterion for the prediction of fat tissue function. They conclude that “creeping fat” may play a protective role during CD and this conclusion is mainly based on observations that adipocytes close to the involved intestine produce more anti-inflammatory cytokines compared to those isolated from distal sites which had a cytokine profile similar to adipocytes isolated from obese patients [78].

Common Features between Intestinal and Mesenteric Inflammation

A key question when considering mesenteric adipose tissue role in IBD pathophysiology is how inflammation in the intestine is related to inflammation in the adipose tissue. Some authors have hypothesized that the first event in CD may not be mucosal damage but translocation of bacteria into the mesenteric tissue leading to chronic inflammation that eventually breaks through as mucosal damage and inflammation [79]. Genetically defective immune responses to commensal bacteria may lead to translocation into the mesenteric fat or inability to clear it, exposing mesenteric adipocytes and preadipocytes to bacteria derived molecules [80] . Genetically predisposed individuals in this model may be individuals with primary macrophage immunodeficiency [81]. The relationship of defective bacterial sensing through NOD1 and 2 to defective definsin production underscores the importance of the mucosal barrier to IBD pathopysiology. In experimental colitis, such as with TNBS or DSS, mucosal damage leads to bacterial translocation to the mesentery precipitating an inflammatory response. PPAR-gamma, realeased in response to bacterial stimuli, up regulates proliferation and differentiation of adipocytes [82], and it is over expressed in the mesenteric adipose of patients with CD [83]. Additionally, if the disease is starting in the mesentery and moving to the mucosa, this would help explain the longitudinal linear mucosal ulcerations along the mesenteric border that have been a morphologic feature distinguishing CD from other forms of intestinal inflammation such as infectious or ischemic causes [84, 85].

Conclusions

Over the last decade the macroscopic, histological and molecular evidence for a potential involvement of mesenteric adipose tissue in IBD pathophysiology are mounting. Although far from a consensus, it is now becoming evident that, at least in the case of "creeping fat" we are faced with a different type of adiposity, with different biochemical properties. There is also evidence to suggest anti-inflammatory and anti-bacterial roles for this tissue during the different stages of CD. The plasticity of adipose tissue, as well as the plurality of the responses that adipocytes have been shown to produce during different pathological conditions, make the aforementioned hypotheses very plausible. Additionally, an important, indirect, obesity-associated, effect of adipose tissue in the outcome of IBD should merit significant consideration due to the inflammatory state and increased levels of circulating risk factors in obese individuals described in this review. Early clinical evidence certainly point to this direction but better controlled studies on animal models are still lacking. As data on adipose tissue physiology and function continue to surface, it is imperative that the adipose tissue question is approached carefully with regard to depot location (it is now well accepted that different fat depots are virtually different mini-organs [86]), size and physiological condition before any conclusions on its potential effects on disease are drawn. Furthermore, the IBD example teaches us that characterization of adipocyte state and size within a depot should precede, and indeed offer a guide for the direction of our studies as they relate to fat tissue contribution in disease pathophysiology. Collectively, these studies underline the importance of adipose tissue for the identification of targets for future, novel therapeutic approaches for IBD. The generation of adipocyte specific study systems is still a work in progress but as more tools (adipocyte-specific vectors, cell lines, animal models) become available that allow for the greater experimental focus on the adipocyte level, important insight on adipose-associated effects on IBD etiology should increase exponentially.

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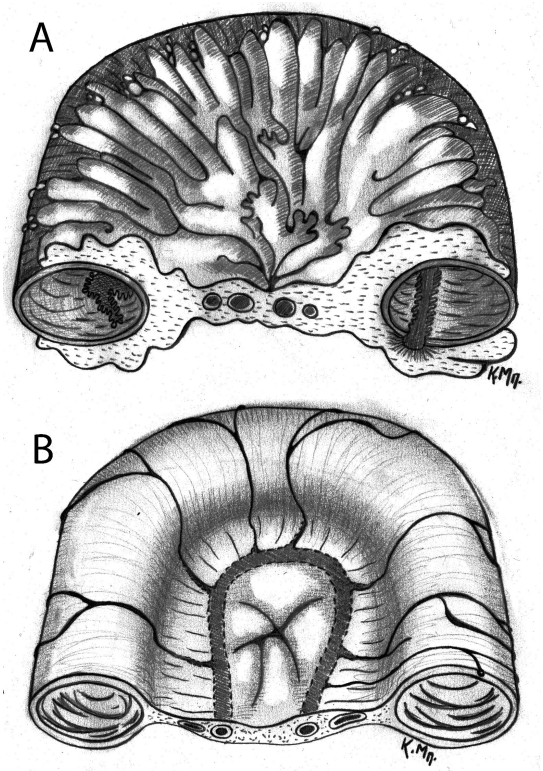

Figure1.
Intestinal cross sections A. depicting fat wrapping during CD and B. normal comparison.

Table 1

Similarities and differences between mesenteric adipose depots in obesity versus CD

	Central Obesity	CD
Adiopse growth by	Hypertrophy[87]	Hyperplasia[84]
Increased BMI	Associated	Not associated
Dyslipidemia	Associated	Not associated
Insulin resistance	Associated	Not associated
Serum CRP	Increased[88]	Increased[6]
Serum TNFα	Increased, produced by stromal vascular cells[13]	Increased, produced by adipocytes[6]
Serum IL-8	Increased[89]	Increased[6]
Serum IL-6	Increased[89]	Increased[6]
Serum leptin	Increased[77]	Increased[47]
Serum adiponectin	Decreased[77]	Increased[46]