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Chapter 8

The Role of Mesenteric Adipose Tissue in Crohn's Disease

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Abstract

Inflammatory bowel disease (IBD) has become an increasingly frequent chronic health problem in the last few decades, particularly in developing countries. In young adults, one of the most common forms of IBD is Crohn's disease (CD). CD is a multifactorial genetic disease characterized by a transmural granulomatous inflammation that especially affects the terminal ileum and the colon. As it involves defective inflammatory pathways, the immune adaptive complex, and environmental factors, this disease has periods of remission and recurrence followed by diarrhea, abdominal pain, and malnutrition, which often lead to lumen bowel stenosis associated to multiple fistulas. In addition, the growth of mesenteric adipose tissue (MAT) near the affected intestinal area is a hallmark of CD. Evidence linking the development of mesenteric and intestinal alterations in CD is increasing. The aim of this chapter is to address adipose tissue in general, the morphological and functional differences between its compartments, the main characteristics of MAT in CD, and its possible role in the etiopathology of this immune-mediated disease.

Keywords: Crohn's disease, inflammatory bowel disease, adipose tissue, mesenteric adipose tissue, inflammation

1. Introduction

Adipose tissue was initially described as an energy storehouse. However, in the last decades, it has also come to be recognized as an endocrine organ with multiple functions. Adipose tissue is composed of adipocytes, connective and nerve tissue, fibroblasts, chondrocytes, osteocytes, myocytes, and immune system cells, which constitute the stromal vascular fraction [1–3].

Adipose tissue is very dynamic, and it is able to secrete a diverse spectrum of biologically active substances designated as adipocytokines, such as cytokines, and hormone-like proteins, such as leptin, adiponectin, and resistin. These substances exhibit endocrine or paracrine functions, and they are important in maintaining energy homeostasis [1, 3–6].

Recent studies have shown that abnormal adipose tissue expansion associated with inflammation predisposes, in turn, to obesity, cardiovascular disease, chronic kidney disease, and inflammatory bowel disease [5, 7–9].

This chapter deals with adipose tissue in general, the morphological and functional differences among its compartments, and presents the main characteristics of mesenteric adipose tissue (MAT) in Crohn's disease (CD), in addition to its possible role in the etiopathology of the disease.

2. Morphological classification of adipose tissue depots

Adipose tissue can be classified into white adipose tissue (WAT), brown adipose tissue (BAT), and the recently discovered beige adipose tissue (BAT) [2, 10].

WAT comprises the vast majority of adipose tissue in the human body. WAT presents an energy-storing property and a secretory function [3–5]. WAT is anatomically divided into distinct depots: subcutaneous and visceral fat [2, 9].

Several studies have reported morphological and functional differences between these adipose tissue compartments. Obese patients have visceral adiposity and are more prone to develop insulin resistance, which strongly correlates with metabolic syndrome. Moreover, the pattern of adipokines secreted by visceral and subcutaneous adipose tissue is different [2, 9, 11].

The importance of anatomical parameters in the regulation of WAT biology is highlighted by the fact that in obese subjects abdominal deep subcutaneous WAT expands much more than superficial subcutaneous WAT [1, 9, 12]. A further instance of this can be seen in that subcutaneous and visceral WAT contribute to cardiovascular disease, whereas femoral WAT may have an overall protective effect. Therefore, changes in biological characteristics of different depots of adipose tissue give rise to different cardiometabolic conditions [9, 13].

Indeed, the heterogeneity among different anatomical depots also appears to stem from their intrinsic diversity, including cellular developmental origin, proliferative capacity, glucose and lipid metabolism, insulin sensitivity, cytokine pattern, thermogenic ability, and vascularization [1, 2, 5].

The features of obesity lie not only in WAT expansion but also in WAT dysfunction associated with qualitative changes in its biological characteristics. In an obese condition, the ingestion of excess nutrients and energy results in hypertrophy, consequent rupturing of adipocytes, and increased local inflammatory cell accumulation, including macrophages, T cells, and altered production of adipokines. These adipose tissue changes and their systemic consequences lead to the concept of obesity as a chronic inflammatory state, and they increase the risk for

multiple chronic diseases, such as type 2 diabetes, cardiovascular disease, several types of cancer, and inflammatory bowel disease (IBD) [1, 3, 5, 9].

At a molecular level, BAT is distinguished from WAT by its expression of uncoupling protein 1 (UCP1), which is crucial to mitochondrial heat production and is involved in the maintenance of body temperature [10, 14, 15]. Neonates exhibit a considerable amount of BAT and a larger fraction of total adipose tissue mass. The thermogenic function of BAT in human neonates has not been yet well assessed due to the absence of safe experimental protocols. Probably, neonates activate a non-shivering thermogenesis (NST) in order to prevent hypothermia [14, 16]. Adult humans exhibit another mechanism to produce heat, and BAT mass seems reduced when compared with neonates. Currently, the activity of BAT in humans shows an inverse correlation to age, body mass index, and the glucose level. Adult humans possess functional BAT in the neck, supraclavicular, and axillary regions, as well as around major vessels, such as the aorta [15, 16].

Thermogenesis is a major function of BAT in rodent and adult humans. Recent advances showed that this tissue may also regulate glucose and lipid metabolism and that it plays a role in regulating energy homeostasis in humans. However, little is still known about secreted adipocytokines in vivo and their role in the regulation of energy metabolism. Studies have shown that transplanted BAT from a healthy mouse into obese-induced and leptin-deficient (ob/ob) mice improves whole-body energy metabolism, increasing insulin sensitivity and reversing preexisting obesity. These effects were accompanied by modulation in the secretion of interleukin (IL)-6, adiponectin, and others cytokines [14, 15].

Recently, another type of adipose tissue, described as beige, has been described. Exposure to cold or to β3-adrenoceptor agonist treatment stimulates WAT. This tissue expresses large amount of UCP1, which can perform a thermoregulatory function. Besides that, beige adipose tissue exists within WAT, mainly in the supraclavicular region, and may be revealed by potent exposure to cold under experimental conditions [10, 14, 15].

Classical brown adipocytes and beige cells play a critical role in the maintenance of body temperature in a cold environment. Therefore, brown and beige adipocytes are promising targets for the treatment of obesity and its related metabolic disorders [10, 14, 15].

Progress in understanding the morphological characteristics of adipocytes, as well as understanding how immune cells contribute to the control of the immunometabolism can provide new potential targets of intervention. The formation of heat-producing beige adipocytes in WAT and the polarization of macrophages transitioning from an inflammatory phenotype toward an anti-inflammatory one are examples of potential targets to explore [5, 10, 14, 15].

Several studies have come out recently concerning the typically increased mesentery in CD (named "creeping fat") near the affected intestinal area. Histological characteristics of the MAT in CD with reduced adipocyte size independent of the weight body have also been reported [17, 18]. However, humoral and cellular changes in this adipose tissue are specific and differ from those observed in hypertrophied fat tissue of obese patients. The functional impact of MAT on CD development and progression is not clear yet and has been studied intensively in recent years.

3. Characteristics of mesenteric adipose tissue and its possible role in Crohn's disease etiopathology

IBD has become an increasingly widespread chronic health problem throughout the last few decades, particularly in developing countries. In young adults, one of the most common forms of IBD is CD. CD is a multifactorial genetic disease characterized by transmural granulomatous inflammation, which affects mainly the terminal ileum and the colon. Defective inflammatory pathways, immune adaptive complex, and environmental factors are involved in CD. This disease presents periods of remission and recurrence followed by diarrhea, abdominal pain, and malnutrition, which often lead to lumen bowel stenosis associated to multiple fistulas [19].

Evidence linking the development of mesenteric and intestinal alterations in CD is increasing. It has been suggested that increased visceral adiposity (of which mesenteric fat is the main component) is pathognomonic of CD. The involvement of MAT is increasingly thought to provide a mechanistic contribution to CD progression. In addition, the increased MAT near the affected intestinal area is considered a hallmark of an active and more aggressive CD [20–22].

For over a century, mesenteric anatomy has been universally depicted in an inaccurate manner. Recent observations confirm a simpler and continuous structure from the duodenojejunal flexure to the mesorectum [23, 24]. In a prospective observational study of a cohort submitted to total excisional surgery of the mesocolon, it was demonstrated that the mesentery binds in all intestinal segments [25, 26]. The mesentery is located between the intestines and the abdominal wall, although the greatest mass of MAT is present in the ileocecal region [23].

This ectopic inflamed tissue in CD patients, also referred as "creeping fat," was already identified by Crohn and collaborators in 1932 [27]. He described its thickening and suggested its possible involvement in CD, even though direct evidence was still lacking. MAT from CD patients presents a large phenotypic variation according to what is observed in surgical specimens, with notorious thickening of adipose tissue near the affected intestinal area when compared to patients who do not present CD. Therefore, surgeons are familiar with the phenotypic variation of the creeping fat, and it is used as an anatomical marker to delineate the extent of active disease in CD patients (see **Figure 1**) [28, 29].

Considering the microscopic appearance of the MAT in CD, the histopathology shows immune cell infiltration, and the adipocytes are smaller (lower mean area and perimeter) than the controls, displaying an intriguing feature [17]. To investigate this morphological feature, apoptosis was studied in these tissues. Analysis by TUNEL assay showed a significantly lower number of apoptotic cells in the MAT of CD when compared to MAT of control group [18]. There was a strong positive correlation between the adipocyte size and the apoptotic index (accessed by TUNEL). In addition, immunohistochemistry for Ki-67 was performed on all MAT samples to access the proliferation rate of the adipocytes. However, no evidence of proliferation was verified in MAT from both groups [18]. In fact, proliferation of adipocytes occurs only in severe obesity, which produces an increased adipocyte count. Surprisingly, we have an interesting situation in CD, in which the tissue looks like a MAT from a severely obese patient, but the proliferation rate is zero. Whether adipocytes migrate to the affected area or mesenchymal cells differentiate to adipocytes/fibroblasts has to be further investigated.

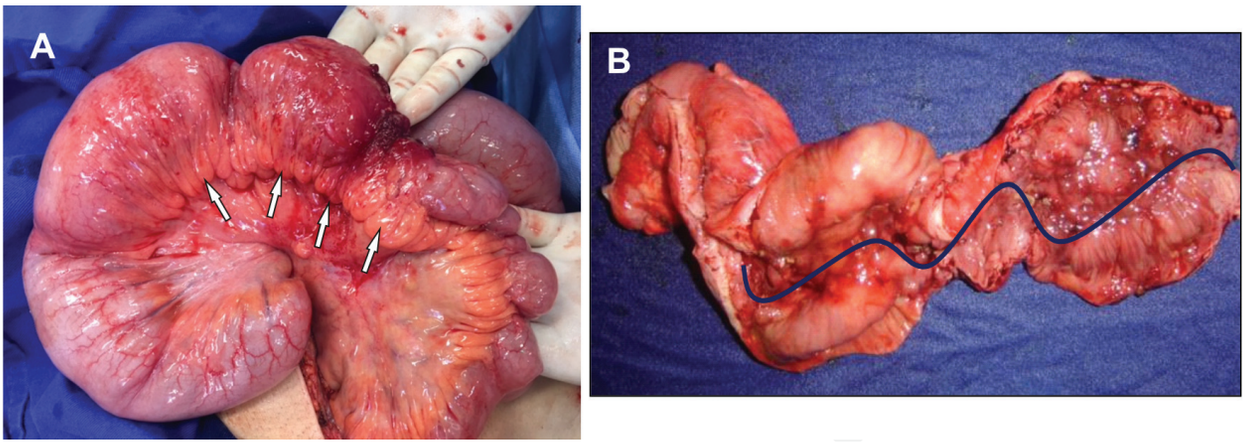

Figure 1. Surgical aspects of creeping fat (mesenteric adipose tissue) in the ileum affected by Crohn's disease. The arrows in (A) indicate the inflamed small bowel surrounded by the creeping fat. The blue line in (B) shows contiguous longitudinal ulcer in the intestinal mucosa localized in the mesenteric face of the bowel (source: Archives of Colorectal Surgery Unit—UNICAMP).

Another microscopic feature is the adipocyte hyperplasia in the submucosa of CD creating a similar histologic feature seen in the mesentery [30]. However, only colonic specimens were evaluated. This characteristic was not verified in samples from ileal CD [31]. For this reason, further investigation is needed, but fibrocytes may play a role in this, for they are increased in the mesentery of CD [32].

Indeed, MAT may present a role in the etiopathology of CD. As it has been demonstrated with other fat deposits, MAT is able to propagate both metabolic and inflammatory signals systemically, potentially modulating clinical features of CD. Its location allows MAT to respond to environmental stimuli and to coordinate intestinal responses locally and systemically [33–35].

The importance of various mesenteric components in the development and maintenance of CD, such as blood vessels, lymph nodes, and nerves, is reported [24, 26, 36, 37]. Although this relationship has not been completely elucidated, some studies provide evidence for the MAT component role in CD, as will be highlighted in the following paragraphs.

A recent study showed the presence of fibrosis, inflamed perivascular, thickened lymphatic vessels, infiltration of stromal cell, perineuronal chronic inflammation, engorgement of vasa recta, and small-sized adipocytes of MAT in patients with active CD [38]. MAT is divided into avascular and vascular regions. Within the vascularized segments, the fibro-adipose tissue involves large vessels and their ramifications [24, 39]. In healthy individuals, the mesentery is soft, and it can be easily separated from the vascularized area. However, when affected by CD, the mesentery thickens, and it interferes in the surgical dissection [28, 29].

Besides these features, histopathological findings, such as vascular lesions, focal arteritis, fibrin deposition, arterial occlusion, and granulomatous vasculitis, are observed in CD patients. These alterations demonstrate the role of mesenteric blood vessels in chronic intestinal inflammation [38, 40, 41]. Changes in vascular endothelium and abnormal leukocyte recruitment were also verified in CD [42]. Moreover, increase in the microvascular density and dysregulated angiogenic activities are other morphological and functional findings in the gut of CD patients [43].

Concerning immune cells, Kredel and collaborators identified an increase of regulatory M2 macrophages in the mesentery of CD, which suggests a protective role of the mesentery in this disease [44].

Zuo and collaborators demonstrated that the function and morphology of the normal MAT in CD patients were similar to control tissues [45]. However, increased MAT adjacent to involved ileum in CD was dysfunctional, exhibiting higher expression of hypoxia-inducible factor 1α when compared to controls, which suggests hypoxia in this tissue.

Moreover, the mesenteric nerves may also influence the pathogenesis, behavior, and prognosis of CD. In an experimental study, functional and structural alterations were observed in the mesenteric nerves of animals with colitis. Mice with colitis induced by trinitrobenzene sulfonic acid or acetic acid presented hyperexcitability of visceromotor neurons causing changes in the lower mesenteric ganglia during the intestinal inflammatory process [38, 46].

4. Molecular characteristics of the mesenteric adipose tissue in Crohn's disease

Recently, studies have highlighted a new function for MAT as an immune organ [47]. MAT's basic cellular components comprise adipocytes, preadipocytes, fibroblasts, mesenchymal stem cells, and endothelial cells. However, when the inflammatory process is initiated, an increase of immune effector cells occurs, including T cells, natural killer cells, and macrophages, as well as innate immune cells [48]. These cells are responsible for the production of several pro- and anti-inflammatory cytokines, such as TNF-α, IL-6, IL-8, IL-23, and IL-10 [49]. Given the potential therapeutic effect of their blockade, a large number of these inflammatory mediators present in MAT and their role in the development of CD have been closely investigated [31].

One of the main pro-inflammatory cytokines in CD is TNF-α. TNF-α has a fundamental role in CD due to the discovery of the therapeutic effect of its blockage [50]. The complete mechanism by which TNF-α regulates MAT inflammation in CD patients has not yet been elucidated, but it is likely a complex and multifactorial process. However, it is known that TNF-α inhibits the proliferation of new adipocytes, which leads to an increased amount of free fatty acids [51].

Another important molecule in the inflammatory process is the peroxisome proliferator-activated receptor (PPAR) transcription factor, which plays an essential role in the regulation of cellular differentiation, development, and metabolism. In CD, it has some specific functions related to the maintenance of the process, such as cytokine production, adipocyte differentiation, fibrocytes differentiation inhibition, and IκB/NF-κB activation [33, 52, 53]. On the one hand, studies have shown a decrease of the PPAR-γ in MAT from CD patients [53, 54]. On the other hand, Desreumaux and collaborators showed that significant accumulation of intra-abdominal fat is associated with overexpression of $PPAR_{\gamma}$ and TNF-α in the MAT of the small bowel mesentery in CD patients, which suggests adipocytes as one of the sources of TNF-α production [55].

Although adipose tissue is able to increase TNF-α secretion via leptin, a hormone produced by adipocytes [56], some studies in the literature did not find high levels of TNF-α in the MAT of CD, neither higher levels of IL-1B, IL6, IL8, IL23, and NF-KB activation [21, 31, 38, 57]. Again, on the

one hand, a decrease NF-kB pathway activation (decreased pIKB/IKB ratio) and increased IL-10 expression in MAT of CD patients have been demonstrated, which suggest a possible anti-inflammatory role of MAT [21, 31]. On the other hand, STAT-1 transcription factor is activated in the MAT of CD patients, suggesting a potential role in the inflammatory process [31]. This topic needs further investigation due these conflicting findings. **Figure 2** summarizes this differential expression of molecular pathways in the MAT and the intestinal mucosa of CD.

In another study, adiponectin, an anti-inflammatory adipokine, was produced and released by adipose tissue that inhibited NF-κB activation in endothelial cells in MAT of CD patients [58]. However, Rodrigues and collaborators obtained low levels of serum and mesenteric adiponectin in MAT of CD, which suggests a defect in this anti-inflammatory pathway, which could in turn help to perpetuate a state of chronic inflammation [17]. Interestingly, all patients had the same BMI, below 25, and this alteration was independent of this parameter and of the presence of metabolic disorders. Resistin, another adipokine, was also studied and was verified to be increased in MAT of CD. Resistin may have a pro-inflammatory role in the MAT and is correlated with increased systemic C-reactive protein in CD patients [59].

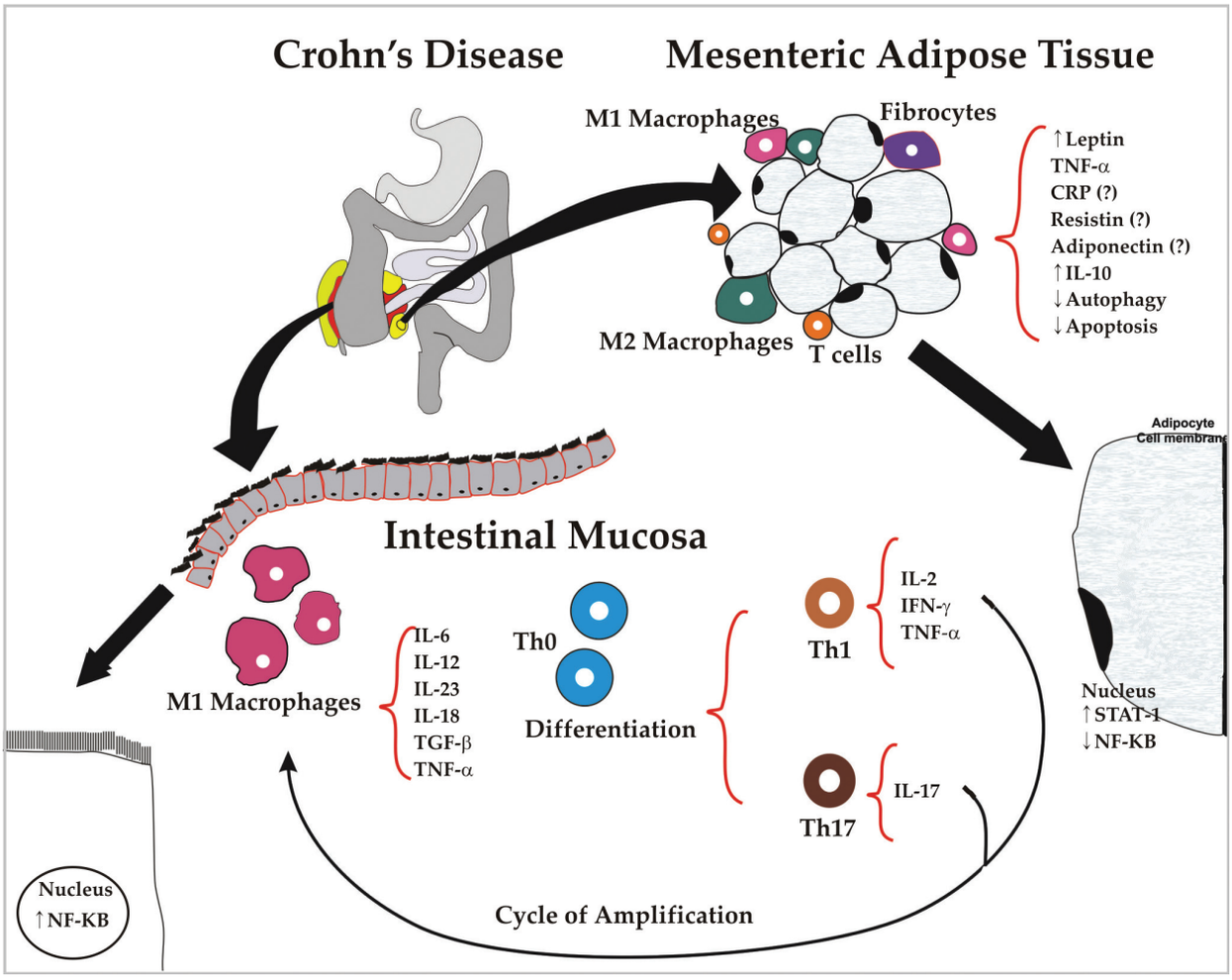

Figure 2. Molecular pathways in the mesenteric adipose tissue and intestinal mucosa of Crohn's disease patients (source: By Support Didactic from the School of Medical Sciences—UNICAMP).

Moreover, the autophagy pathways have been addressed in the last few years; for this process, it is crucial for mucosal immunity, and there is a growing number of autophagy-related genes associated with the development of CD [60–62]. Leal and collaborators demonstrated a reduction in autophagy markers in MAT of CD patients, which may maintain the inflammatory response in the affected intestine [63]. In this study, LC3-II protein, which is indispensable for the formation of autophagosome, was lower in the MAT of CD, suggesting an impairment of the autophagy process in this tissue. The altered autophagy could lead to unprocessed unnecessary protein accumulation, which activates pro-inflammatory pathways implicated in the pathogenesis of CD.

5. Conclusions

MAT may have an important role in CD inflammation, for it was possible to observe an altered balance between pro-inflammatory and anti-inflammatory factors in this tissue, decreased apoptosis, as well as defective autophagy. Available data indicate that mesenteric changes are primarily anti-inflammatory but can ultimately cause inflammation in CD. Currently, the mesenteric events in the chronology of CD are under discussion. MAT may be involved in the maintenance of inflammation in the late stages of the disease and in the mechanism that leads to relapses during the course of the disease. Moreover, the interaction between cytokines, adipokines, transcription factors, adipose stem cells, vascular endothelia, and adipocyte plasticity may imply in MAT remodeling, which certainly influences CD physiopathology.

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Conflict of interest

The authors declare that they have no conflict of interest.

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