BBA - Molecular Basis of Disease 1865 (2019) 63–72

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

Review

The role of obesity in inflammatory bowel disease☆

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ARTICLE INFO

Keywords:
Adipocytokines
Adiponectin
Inflammation
Bowel disease

ABSTRACT

In just over a generation overweight and obesity has become a worldwide health concern. The ramifications for this on future health care costs and longevity are consequent, whilst increased adiposity is a harbinger for diabetes, kidney and bone failure, and cancer. An area of intense interest where the role of adiposity is avidly discussed is in inflammatory bowel disease (IBD), which presents mainly as Crohn's disease (CD) and ulcerative colitis (UC). Studies in patients associating IBD with a western diet are divergent. Nevertheless, elegant studies have found gene polymorphisms in humans that in murine models parallel the inflammatory and gut microbiome changes seen in IBD patients. However, an area not to be ignored are the alterations in adipocyte function with ensuing adiposity, in particular and a focus of this review, the dysregulation of the levels of adipocytokines such as leptin and adiponectin. Herein, we present and discuss the known influences of a western diet on IBD in patients and rodent models and how adipocytokines could influence the IBD disease process.

1. Introduction

A global study established that between 1980 and 2008, the average body mass index (BMI) increased by 0.5 kg/m^2 per decade, bringing to 1.46 billion the number of adults overweight worldwide [1]. This trend has continued and in 2016 the World Health Organization published that more than 1.9 billion or 39% of the adult world population, and 381 million children and adolescents were overweight [2]. This pattern is not just associated with industrialized countries such as Northern America and Western Europe, but has grown to include low and middle-income countries, where the lifestyle is becoming Westernized [3]. Significantly, obesity parallels severe inflammatory associated health disorders that include type-II diabetes and cardiovascular diseases, and is increasingly related to cancers of the liver, breast, kidney and colon [4,5].

A harbinger for colon cancer is inflammatory bowel disease (IBD), that includes Crohn's disease (CD) and ulcerative colitis (UC). People afflicted by IBD are chiefly found in North America and Europe, where it has been estimated that 1.4 and 2.2 million people suffer from CD and UC, respectively [6,7]. However, its incidence and prevalence is now increasing worldwide, particularly in paediatric and non-European ancestry populations [8]. Given that IBD is predominantly found in industrialized regions of the world, it suggests that environmental factors, for example a sedentary lifestyle and diet with genetic risk factors are influencing disease development and progression [9–12]. A correlation between being overweight or obese and an increased risk of IBD is a contentious subject, but warrants closer inspection, as there are implications for health care costs and economic productivity. Therefore, in this review we will discuss the layers of evidence, both positive and negative, concerning the relationship between obesity, genetics and IBD.

2. Clinical studies examining the association of obesity with IBD

The growth in IBD incidence is speculated to come from altered environmental factors, such as a sedentary lifestyle and hyper-nutritional diet and their influence on host genetics. Obesity is a growing public health issue in many Western countries and we will therefore consider reports that have examined the association of being overweight or obese with IBD.

Studies have demonstrated positive relationships between obesity and IBD risk. By example, a United Kingdom (UK) study of 524 IBD patients demonstrated an association between obesity at diagnosis for CD but not with UC. They found increasing BMI, as a measure of weight gain to parallel an increasing risk of CD. Additionally, they observed a 'dose response' relationship, where a low BMI associated with reduced

☆ None of this material has been published or is under consideration elsewhere.

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https://doi.org/10.1016/j.bbadis.2018.10.020
Received 11 June 2018; Received in revised form 27 September 2018; Accepted 16 October 2018
Available online 22 October 2018
0925-4439/

CD and increased UC risk, leading the authors to suggest that obesity may be associated with a distinct form of CD [13]. Staying in the UK, a Scottish cohort of 1269 patients revealed 52% of the CD group were overweight or obese, and surgery rates for this group were 8-fold greater than CD patients with normal weight [14]. A US based study undertaken by Khalili et al., considered 111,498 women beginning at ages 18–20 and followed-up over 18 years, and found that increasing weight gain was associated with an elevated risk of CD [15]. In contrast to these findings, population studies have also illustrated less pronounced associations. An Irish study of 100 patients, reported a high prevalence of overweightness (40%) among CD patients, and within this cohort they observed lower disease activity and no increased need for surgery [16]. A study from the European Prospective Investigation into Cancer and Nutrition (EPIC) followed 519,978 men and women from ten European countries, and no correlation between being overweight or obese and the development of either CD or UC was observed [17].

Taken together, the data concerning the relationship between IBD and being overweight or obese is inconclusive, with both small and large population studies of differing demographics demonstrating positive or negative associations. However, despite this conclusion evidence concerning specific dietary factors that are present in a western diet has illustrated links with IBD. These we will now discuss.

2.1. Dietary links with IBD

As increased weight is a product of excess nutrition, dietary components have also been considered in IBD. A Japanese study investigated the change in dietary composition from the traditional vegetable food to a high fat western diet on CD risk. It showed that CD incidence correlated with increased dietary intake of total fats, animal fat, n − 6 polyunsaturated fatty acids (PUFA), animal protein, milk protein, and the ratio of n − 6 to n − 3 fatty acid intake. In contrast, CD risk was not correlated with the intake of fish protein, and was inversely correlated with vegetable protein intake [18]. Separately, a detailed systematic review of 19 studies representing 1269 CD and 1340 UC patients and dietary intake, associated increased UC risk with a high intake of total fat, PUFAs, omega-6 fatty acids, and meats, and CD with a high intake of PUFAs, omega-6 fatty acids, saturated fats, and meat. In contrast, a reduced risk of CD, but not UC, correlated with a high intake of dietary fibre and fruits. No association was noted between total carbohydrate intake and IBD risk [19]. A US based study used two large well characterised groups of women that had provided long-term information of their intake of fat, and diagnosis of CD and UC. Here it was found, that total fat, saturated fats, unsaturated fats, n − 6 and n − 3 PUFAs were not associated with an increased risk of CD or UC. However, long-chain n − 3 PUFA intake correlated with a trend towards lower UC risk, and in contrast, trans-unsaturated fatty acid intake was associated with a trend towards increased UC incidence [20].

2.2. Dietary behavioural changes in IBD

Apart from the difficulty in stratifying human data, caution must also be given to the behavioural changes that IBD often induces while this can create statistical bias. Diagnosis of IBD can take several months, and due to their apparent digestive problems, patients adapt their diet. An Italian group followed 83 patients newly diagnosed with IBD (41 UC and 42 CD), and due to their symptoms changes in dietary habits were reported by 39% of patients. There was a positive relationship between the intake of margarine and a non-significant trend for pasta and rice in UC, and meat and cheese in CD. In addition, IBD patients reported a significant decrease in the intake of potatoes and fish, and CD patients reduced vegetable and tuna fish consumption compared to healthy controls. The authors also found a dietary pattern for patients having IBD, which is composed of pasta, red meat, sweets, butter and margarine [21]. An Israeli group followed a similar approach, questioning newly diagnosed patients on their pre-illness diet. The group was made of 87 patients, 60% males and with an average age of 30 years. They found that sugar consumption was associated with increased IBD risk. Total energy consumption was not associated with IBD, however fat consumption strongly correlated with IBD risk, and was found for all types of fat, vegetable, animal, saturated and unsaturated, and was highest for cholesterol in patients with UC [22].

Table 1
Publications describing an association between obesity and IBD in patients.

	Ulcerative colitis	Crohn's disease	Outcome
BMI HFD	No correlation [19] [21] [22]	[13] [14] [15] [18] [19] [21] [22]	BMI correlated, dose response • CD: saturated fats – MUFAs - ω-3/−6 PUFA - cheese • UC: total fats - ω-6 PUFA - margarine

Taken together the population data correlating diet and food intake with increased IBD risk is diverse (Table 1). Possible cofounders contributing to this data could be explained by the variety of measurement methods, different ethnic groups, heterogeneous genetic backgrounds, the presence of underlying disease, and for this reason further studies are required to better stratify and define the relationship between diet type and IBD.

3. Possible promoters of inflammatory bowel disease (IBD)

Given the above, what setting in a host can promote increased IBD risk in the presence of an energy dense western diet? Notably, different population groups have lower IBD rates and this parallels particular bacterial species and dietary consumption. To address this, studies have focussed on the composition of the microbiome across population groups, where IBD is less or more prevalent and examined the effect of diet on the bacterial species present.

The human gut is filled with trillions of microorganisms and the most prevalent bacterial species are *Bacteroidetes* and *Firmicutes* [23]. A study by De Filippo and colleagues compared the gut microbiota of two groups of children coming from an African rural village and Florence, Italy. The diet of the African group was mostly vegetarian, rich in fibres and plant polysaccharides, whereas the Italian diet contained predominantly fat and animal proteins. The faecal microbiota of the African cohort consisted of a large quantity of *Bacteroidetes* and reduced *Firmicutes*, together with an abundance of *Prevotella* and *Xylanibacter* bacteria, that are known to digest cellulose and promote uptake energy. In contrast, the Italian children had an abundance of *Firmicutes* and limited numbers of cellulose degrading bacteria species [24]. Subsequent studies have established differences in gut microbiome between geographic regions and age [25,26]. Moreover, apart from geographical differences, the gut microbiome and energy produced is influenced by diet. By example, during obesity, the proportion of *Bacteroidetes* and *Firmicutes* is reversed and *Firmicutes* levels increased by 50% [27], and the microbiome has a greater capacity to generate energy from food compared to lean individuals [28].

Considering that the above, alterations in the metabolic products of gut microbiota has been described to modulate the integrity of the epithelial layer and the gut immune response. An important contributor is butyrate a short-chain fatty acid (SCFA), that is a product of plant polysaccharides fermentation [23]. A low concentration of butyrate, enhances the integrity of the intestinal barrier, whereas a high concentration promotes epithelial cell death [29,30]. The production of another SCFA, acetate increases protection against the enteropathogen *Escherichia coli 0157:H7* by maintaining epithelial barrier function and restricting the translocation of bacterial toxins to the blood supply [31]. Mechanistically, a study by Maslowski et al., demonstrated that the binding of SCFA to the G-protein coupled receptor 43 (GPR43) resolved inflammatory responses in colitis, arthritis and asthma, whereas,

GPR43 deficient mice had increased inflammation [32]. *Helicobacter hepaticus*, a commensal bacterium can promote colitis in mice. This effect was ablated by the addition of *Bacteroides fragilis*, due to the production of a single polysaccharide A (PSA), while mice provided with purified PSA showed reduced inflammation [33]. These results show that molecules produced by the bacterial microbiota can modulate the balance between colonic health and disease. Consistent with this data and translating to IBD patients, the microbiota of CD and UC patients has been shown to differ substantially to non-IBD controls. Specifically, it has been observed in one IBD cohort that *Bacteroidetes* and SCFA producing bacteria are depleted, and *Actinobacteria* and *Proteobacteria* are increased [34]. These data also suggest that possible treatment strategies for some forms of IBD could be accelerated by resolving the microbiological imbalances.

Taken together these results show that diet modifies the natural microflora and creates dysbiosis. This in turn promotes an inappropriate inflammatory response leading to an imbalance in local pro- and anti-inflammatory factors and become a factor in promoting IBD [35]. Nevertheless, as shown above given the inconclusive clinical data connections between obesity and IBD in patients, it is arguable that dysbiosis generated through a western diet is not the only factor. A possible and additive scenario through which IBD risk could ensue is in individuals with inherited genetic mutations, that in the presence of a western diet lead to altered immune responses and increased intestinal permeability.

4. Genetic change linked with promoting IBD

Independent of being overweight and obese, numerous genetic studies, such as through genome-wide association studies (GWAS) and meta analyses, have revealed genetic mutations that represent four broad mechanisms that are important for IBD pathogenesis, namely inflammation linked with microbial sensing, tight junction connections between epithelial cells, autophagy, and endoplasmic reticulum stress, and importantly for some of these genes that we will consider there is a convergence of these mechanisms.

Large population cohorts with IBD have been examined for genetic mutations through GWAS [36]. A meta-analysis of six GWAS for UC resulted in the identification of candidate genes that could provide important insights into the disease process. Some of these included components of the immune system: interleukin 1 receptor (IL1R2); two receptors for interleukin-8 (IL8RA/B); interleukin-7 receptor (IL7R); interleukin-12B (IL12B); PR domain containing 1 (PRDM1), a master transcriptional regulator of plasma cells and a transcriptional repressor of the interferon-β (IFN-β) promoter, and cell adhesion: guanine nucleotide binding protein (G protein) alpha 12 (GNA12), a membrane bound GTPase that plays an important role in tight junction assembly in epithelial cells [37].

A meta-analysis of six CD GWAS demonstrated loci that are associated with the disease, and included Mothers against decapentaplegic homolog 3 (*SMAD3)* which mediates transforming growth factor-β signalling; *IL-10* which can inhibit the synthesis of pro-inflammatory cytokines within macrophages and T_h1 cells; interleukin-2 receptor A (*IL2RA)* which mediates IL-2 signalling in host defence; tyrosine kinase 2 (*TYK2*) a member of the JAK-signal transduction family; DNA methyltransferase 3a (*DNMT3a*) a key methyltransferase genes in humans - effecting epigenetic regulation of gene transcription by methylating cytosine residues within CpG islands; and T-cell Activation GTPase-Activating Protein (*TAGAP*), which is associated with multiple autoimmune diseases [38]. More recently, a large study using the DNA from near 30,000 patients, including approximately 17,000 with CD and 13,000 with UC, reclassified IBD into three new groups: ileal Crohn's disease, colonic Crohn's disease and ulcerative colitis, on the basis of the genetic risk [39].

Taking such studies on board, has in turn led to the molecular analyses of specific genes. One of the first genes linked to increased IBD risk is Nucleotide-binding oligomerization domain-containing protein 2 (*NOD2)*. NOD2 is a pathogen recognition receptor and is located in Paneth cells. It is involved in the activation of the immune system *via* the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway [40]. Mutations in *NOD2*, result in an altered signalling cascade and this has been shown to be associated with CD [36]. In murine models, *NOD2* ablation makes mice more susceptible to colitis and have an elevated inflammatory response to bacteria, and the transfer of gut bacteria from *NOD2*-knock-out mice to wild-type, increased their risk of colitis [41–43]. Indeed, in IBD patients with *NOD2* mutations, *Escherihic coli* which are a major member of the Enterobacteriaceae family of gram negative bacteria, were found in greater number [44].

An example of another significant gene is caspase recruitment domain-containing protein 9 (*CARD9)*. The mechanism of action is through the glycoprotein C-type lectin Dectin-1 (*CLEC7A*) that recognises β-1,3-glucans from fungal cell walls, that in turn transmits a signal through CARD9, which is a positive regulator of apoptosis and activates the innate immune system *via* NF-κB signalling [45,46]. Moreover, CARD9-null mice have increased numbers of fungal species that are typical of dysbiosis in IBD and fail to metabolize tryptophan into metabolites that act as aryl hydrocarbon receptor (AHR) ligands. The AHR system is important in inhibiting inflammation by upregulating interleukin-22 (IL-22) and limiting T helper 17 cell (T_h17) responses, to maintain muscosal barriers and promote the clearance of pathogens. Importantly, in some IBD patients with CARD9 mutations, the microbiota produce less AHR ligands [47–49]. In addition, Clec7a knock-out mice were found to be resistant to both dextran sodium sulfate (DSS) and T cell-induced colitis. The colons of the knock-out mice had increased levels of *Lactobacillus murinus* leading to the expansion of T regulatory (Treg) cells and their production of interleukin-10 (IL-10) and interleukin-17 (IL-17). The administration of laminarin, a Dectin-1 antagonist, into WT mice suppressed the development of DSS-colitis, and was associated with increased levels of *Lactobacillus murinus* and Treg cells. In patients *Lactobacillus murinus* were rarely detected in the faeces, however the levels of *Lactobacillus salivarius* a related species was decreased in CD patients, had protective immune responses, and suggests that *Lactobacillus salivarius* may be protective for IBD [50].

ER stress signalling concerns a cells ability to cope with increased levels of misfolded and unfolded proteins through a lengthy signalling pathway termed the “the unfolded protein response” (UPR). Normally, the activation of the UPR ceases protein translation, promotes the degradation of the unwanted misfolded/unfolded proteins, and increases the generation of molecular proteins called chaperons to assist in protein folding, and when the UPR function is overwhelmed, an inflammatory response and apoptosis is induced by UPR related mechanisms [51]. In inflamed intestinal epithelial cells, ER stress is increased, and the transcription factor X-box-binding protein 1 (XBP1) has been shown to mediate these events in IBD. The absence of *XBP1* in the colons of mice results in ER stress, inflammation and the apoptosis and loss of Paneth cells. Significantly, *XBP1* deficiency results in enhanced inflammatory responses after normal mucosal inflammatory insults, and increased experimental colitis on DSS treatment. The same group, also showed that in CD and UC patients, ER stress is present and *XBP1* levels are elevated, and *XBP1* single nucleotide polymorphisms are associated with IBD [52].

Another aspect modulating the immune response is the deterioration of the mucosal barrier that covers the epithelial layer of the gut. The intestinal epithelium is covered by a protective viscous layer that contain primarily mucus glycoproteins, which are secreted by the Goblet cells. Patients with IBD often have insufficient mucus and hence increased presence of mucolytic bacteria. A major gene that makes this layer is *Muc2* [53]. In the colon, Muc2 is responsible for two layers, a stratified inner, firmly attached mucus layer (s) and an outer, non-attached mucus. Mucins are glycoproteins that carry large amounts of O-

linked oligosaccharides (O-glycans), which constitute up to 80% of the mass of the mucin molecules. O-glycans are synthesized post-translationally and through the action of core 1-β1,3-galactosyltransferase (*C1galt1*) are attached to the mucin protein backbone in the Golgi apparatus [54]. The high glycosylation of Muc2 makes it very hydrophilic, giving it a gel-like net structure, and is size selective as bacteria cannot diffuse through it, making it a protective barrier above the epithelial layer [55]. However, if the mucosal barrier is weakened, micro-organisms can enter and contact the epithelium and induce an immune response [56]. At this point, macrophages, neutrophils and T cells can infiltrate the epithelial layer and produce inflammatory cytokines. These can in turn weaken the tight junctions that hold the epithelial cells together, making the epithelial layer more fragile and permeable [57,58].

Studies using Muc2 deficient mice show that they spontaneously develop colitis by 5 weeks of age and treatment with dextran sulfate sodium (DSS) worsened the symptoms [59]. Over time untreated $Muc2^{-/-}$ mice have spontaneous intestinal tumour formation with progression to invasive carcinoma [60]. In a similar vein, a mouse model developed through treatment with the DNA mutagen *N*-ethyl-*N*-nitrosourea produced a murine model known as *Winnie* mice [61]. These mice spontaneously developed colonic damage and inflammation, with numerous similarities to human UC and are very susceptible to induced inflammation. The primary driver in this model was a single missense mutation in *Muc2* leading to the hyper oligomerisation and accumulation of Muc2 in the endoplasmic reticulum and the induction of the unfolded protein response (UPR) [62,63]. Similarly, mice that lack intestinal specific *C1galt1* develop spontaneous colitis. In IBD patients, polymorphism in a number of MUC genes are associated with increased IBD risk [64], and intestinal disorders including enteric infection, colon cancer and aging (reviewed in [65]). An important attribute of mucins is the use of interchain disulphide bonds to stabilise the net-like structure [66]. A recent report has shown that some gut bacteria produce sulphide that can reduce the disulphide bonds in the mucus, to denature the mucin network and increase bacterial access to the mucus layer [67]. Subsequent treatment with antibiotics eliminated the respective sulfide-producing and mucin-degrading bacteria.

Autophagy is a cellular lysosomal pathway that removes damaged or excessive protein products or organelles, and is important in the providing energy and maintaining protein quality, and in the immune system to remove pathogens [68]. GWAS published in 2007 showed associations with Autophagy related protein 16-1 (*ATG16L1*) and immunity-related GTPase family (*IRGM*) in CD [69,70]. Gene variants in ATG16L1 result in irregular Paneth cell structure and function and reduced uptake of bacteria, and similarly a reduction in *IRGM* expression correlates with reduced autophagy and pathogen clearance [71,72]. Returning to *NOD2*, it has been shown to be at the nexus of inflammation and autophagy, and is critical for the autophagic response to invasive bacteria. Specifically, Nod2 recruits ATG16L1 to the plasma membrane and is required for the clearance of intracellular pathogens. In CD genetic variants of both *NOD2* and *ATG16L1* have been recorded and mechanistically promote a deficiency in the autophagic clearance of pathogens [73,74].

An important protein involved in cell-cell adhesion is epithelial-cadherin (E-cadherin; *CDH1*). E-cadherin is involved in key morphogenetic processes such as cell growth, epithelial differentiation, and proliferation [75]. Genetic studies have shown that truncated forms of E-cadherin are associated with Crohn's disease, and intestinal biopsies from patients with Crohn's disease carrying these mutant alleles show inappropriate protein localization and cytosolic accumulation of E-cadherin [76]. The nuclear transcription factor, hepatocyte nuclear factor 4α (*HNF4α*), modulates the expression of several genes involved in metabolism, cell junctions, differentiation and proliferation in the liver and intestinal epithelial cells. HNF4α is down-regulated in patients with IBD and mice with specific intestinal epithelial cell removal of *Hnf4α* are more susceptible to chemically induced colitis, indicating HNF4α is necessary for intestinal barrier function [77–79].

Taken together genetic polymorphisms and subsequent murine studies have linked genes involved with inflammation, autophagy, endoplasmic reticulum stress, barrier function and cell adhesion with IBD. Nonetheless, as discussed in the aforementioned sections, the correlation between increased body weight and human IBD risk is poor. However, IBD can progress to colitis-associated colorectal cancer (CRC), and is responsible for 10–15% of all deaths among IBD patients [80]. Additionally, overweight and obese individuals have an increased risk of developing CRC, and the number of patients diagnosed with CRC is increasing [81–84]. However, the genetic changes that have been described as causative factors for increased IBD risk have been in humans for millennia. Therefore, apart from genetic change and bacterial type being associated with IBD, there must be other causative effectors that a western diet and obesity dysregulate. The evidence for this we will now consider.

5. Experimental evidence for a western diet as a risk factor in IBD

Since the data concerning links with adiposity and IBD in humans is inconclusive, mouse models have been developed to explore this relationship. Ma and colleagues fed C57BL/6 mice either a high-fat diet (HFD) or a normal chow, and then exposed them to DSS to induce colonic inflammation. The HFD fed mice had shorter colons, more inflammation and greater weight loss than their normal chow counterparts. In addition, they observed that HFD mice had greater numbers of non-CD1d-restricted natural killer (NK) cells, and they expressed more tumour necrosis factor (TNF-α) and interferon (IFN-γ). HFD mice also had decreased levels of colonic immunosuppressive T regulatory cells (Treg), and the depletion of colonic NK T cells or the adoptive transfer of Treg cells reduced DSS colitis in HFD mice, and TNF-α and IFN-γ expression [85]. Similarly, Cheng et al., fed mice a low fat (LFD) or HFD diet and then treated them with 2% DSS for 7 days. They observed that HFD/DSS mice developed more severe colitis as shown by shorter and more damaged colons, epithelial loss, and an increased inflammatory response, compared to LFD/DSS mice [86]. An additional study, showed alike pathology findings with an increased inflammatory infiltrate consisting of macrophages, neutrophils and lymphocytes in both the colon and visceral adipose tissue (VAT) of the DSS HFD group. They found as well in the adipose tissues increased levels of Toll like receptor 4 (TLR4), IL-6 and TNF-α, showing that a HFD promoted inflammation in the fat deposits and colon [87]. In contrast, to illustrate the favourable aspects of a high fibre diet on colitis outcome, a Korean group fed mice a HFD in combination with a normal raw diet (NRM), consisting of dried fruits, vegetables and brown rice. They showed that the NRM, was protective against colitis, reducing colonic shortening, damage and the infiltration of inflammatory, and the serum levels of IL-6, TNF-α and IL-1β [88].

To investigate a potential mechanism through which a HFD diet promotes intestinal inflammation in mice Gulhane et al., observed that a HFD increased endoplasmic reticulum (ER) and oxidative stress, and reduced mucosal barrier integrity as exemplified by reduced Muc2 and claudin-1, and increased serum endotoxin levels [89]. In cultured intestinal cells, non-esterified long-chain saturated fatty acids increased oxidative and ER stress, and the intracellular aggregation of Muc2, illustrating an UPR response. Previous studies by the same group showed that interleukin 22 (IL-22) can suppress oxidative and ER stress in pancreatic β cells, by activating the antioxidant pathway and repressing the pathways promoting reactive oxygen and nitrogen species, to restore insulin secretion [90]. They therefore treated epithelial cells and *Winnie* mice with palmitate or HFD respectively with IL-22, and observed that IL-22 reduced oxidative and ER stress, and inflammation. Importantly, IL-22 therapy in HFD mice, resulted in the dose-dependent reduction in the extent of *Escherichia coli*, and this was associated with decreased serum endotoxin levels [89]. Collectively, these experimental data illustrate that a HFD can promote inflammation, ER stress and

reduced epithelial barrier integrity in rodents, similar to but independent of the genetic changes observed in IBD patients. It is plausible that rodents due to their evolution and normal dietary intake are more susceptible to the induction of IBD by a HFD, whereas in contrast in humans who are omnivores are more resistant to a HFD, and hence additionally require genetic alterations and dysbiosis to promote IBD. Nonetheless, another possible modulator of colon integrity and promoter of IBD in patients and in rodent models, is the indirect action of the expanded fat mass, this we will now consider.

6. Adipocytes and their functional roles in IBD

The adipose tissue is composed of white adipose tissue (WAT) and brown adipose tissue (BAT). The WAT chiefly contains adipocytes, which store fat molecules depending on the needs of the body through lipogenesis and lipolysis [91]. Under normal conditions of equal energy consumption and expenditure, lipogenesis and lipolysis are balanced and fat does not accumulate. During excess nutrition, adipocytes undergo hypertrophy until they reach a threshold size, and hyperplasia is then triggered and pre-adipocytes differentiate into mature adipocytes [92]. The rapid expansion of the adipose tissue results in poor vascularisation and cellular apoptosis, which promotes hypoxia to stimulate angiogenesis, and macrophages infiltrate the adipose and form crown-like structures around the dead cells, and release inflammatory cytokines, such as TNF-α and IL-6 [93–96]. Additionally, inflammatory ligands like lipopolysaccharide (LPS), activate receptors such as the Toll-like receptor (TLR) and subsequently stimulate the NF-κB pathway to further reinforce inflammatory cytokine production [93]. Importantly, the WAT also has active endocrine activity, and as adiposity increases, the secretion of growth factors known as adipocytokines, the majors being leptin and adiponectin (APN), becomes dysregulated. Both these have defining roles in promoting insulin resistance, the metabolic syndrome, modulating inflammation, cardiovascular dysfunction and hepatic disease [97]. The mechanistic roles of leptin and adiponectin (APN) in IBD are only beginning to be understood, thus we will now consider the published evidence and what this may mean for the field.

6.1. Leptin

Leptin is a 16 kDa peptide secreted by WAT and has receptors in the brain and peripheral tissues and has activity and in the endocrine system, reproduction and immunity. In the immune system leptin has pro-inflammatory functions, by example, it can limit the proliferation of memory T cells, enhance naive T cell activity and promote the polarization of $CD4^+$ T cells into Th1 while suppressing Th2; leading to the secretion of TNF-α and interferon gamma (INF-γ) [98]. Leptin levels can also be increased by inflammatory stimuli, such as interleukin-1(IL-1), IL-6, lipopolysaccharide (LPS) or bacterial infection [99]. Apart from these functions, leptin is involved in the transmission to the brain of the amount of energy that is available and can regulate food intake [100]. Significantly, leptin concentrations vary throughout the day, with the highest concentration occurring between midnight and early morning and a low concentration in the afternoon [101]. Comparing obese and lean individuals, the pattern of leptin production is alike, except that obese patients have greater peaks and higher leptin concentrations [102]. During fasting, the leptin concentration drops to reduce metabolism and limit energy consuming growth-processes [103,104]. Given that the circulating levels of leptin are increased during obesity and bowel inflammation, studies have sought to address Leptins's function in IBD.

6.2. Adiponectin

The most abundant adipocytokine is adiponectin (APN) and its secretion and plasma concentrations are reduced with increasing adiposity [105]. Human APN is a 244 amino acid, 30 kDa protein consisting of three domains; a signalling peptide, a collagen-like motif and a globular domain, and circulates in the serum in different molecular forms: a low molecular weight (LMW) trimer, a middle molecular weight (MMW) hexamer, and high molecular weight (HMW) multimers, considered to be the most biologically active [106]. APN binds to three cell surface receptors, the G-protein like transmembrane receptors AdipoR1 and AdipoR2, which are expressed mainly in the skeletal muscles and liver, and T-cadherin, a cadherin molecule linked to the membrane *via* a glycosyl-phosphatidylinositol (GPI) anchor. T-cadherin is found in endothelial, epithelial, muscle and smooth muscle cells and is also involved in calcium-dependant homophilic signalling cell interactions. APN signalling is myriad and is involved in regulating metabolism through adenosine monophosphate-activated protein kinase (AMPK) to enhance insulin sensitivity. APN through AMPK can also hinder acetyl-CoA carboxylase action, the enzyme that produces malonyl-CoA as a substrate for FA biosynthesis, and increase fatty acid breakdown [107,108]. APN can also restrict the anti-apoptotic and pro-inflammatory actions of NF-κB [109]. Given these important metabolic and anti-inflammatory roles, low levels of serum APN have been linked to malignancies such as breast [110], liver [111] and colon cancer [112], and hepatic disease, as recently reviewed [106]. Thus, in the context of being overweight and obese, leptin and adiponectin levels become increased and decreased, respectively.

6.3. Clinical and experimental data examining leptin and adiponectin in IBD

Clinical studies examining the association of serum leptin levels in IBD is contrasting, as elevated [113–115], reduced [116,117], and unaltered levels [118,119] have been associated with IBD. Similar to leptin, the data concerning APN and human IBD are divergent. Reports show that serum APN levels are decreased [114,118], increased [116,120], or not related [117,121]. The discrepancy in these results could in part be explained by small data cohorts used in some of the studies, adequate controls and treatment status of the patients. However, in considering the mesenteric fat the data becomes further difficult to interpret, as studies have illustrated increased leptin expression parallels inflammation and IBD in patients [122,123], and rodents [124], and APN levels are increased [125], and linked with colonic inflammation.

In murine models, leptin deficient (*ob/ob*) mice after DSS or trinitrobenzene sulfonic acid (TNBS) treatment were resistant to colitis, had significantly reduced colonic inflammation, and treatment including recombinant leptin stimulated intraepithelial lymphocytes (IELs) and lamina propria mononuclear cells (LPMCs) *in vitro* and promoted colitis *in vivo*, showing that leptin deficiency accounted for the phenotype [126]. A subsequent study by the same group, illustrated that the transfer of leptin receptor deficient lymphocytes into severe combined immunodeficiency (*SCID*) mice delayed intestinal inflammation compared to wild-type, emphasising that leptin acts on T cells to promote inflammation. In the context of IL-10, whose loss is associated with increased murine colitis, *ob/ob* IL-10 double knock-out mice had similar inflammation and colonic damage as in IL-10 KO mice [127].

In models using APN-KO mice the data have been contradictory. Nishihara and co-workers observed that APN-KO mice were more susceptible to colitis on DSS treatment, and presented with enhanced inflammation and elevated IL-1, IL-6, and TNF [128]. DSS treatment combined with an adenovirus overexpressing APN limited colitis in both WT and APN-KO mice. In contrast, Fayad et al. (51, 52) reported that APN absence and DSS treatment protected against colitis, and reduced inflammation was observed. These non-convergent data could be explained by methodological differences, the source of KO mice, the form of recombinant APN, and the pathogen status of the animal facilities.

To rule out these differences, we recently undertook a study with age-matched littermate wild-type and an established line of APN KO

mice, that confers many of the published functions of APN [129]. We found that APN KO mice had worse colitis and an enhanced immune response after DSS treatment. Surprisingly, no other study had thoroughly investigated adiponectin's function on the colon epithelial cells and immune system. We found that adiponectin supported epithelial cell growth through AdipoR1 as its absence promoted apoptosis in *in vitro* models. Concerning the immune system, increased activation of signal transducer and activator of transcription 3 (STAT3) and numbers of activated B cells were found in APN KO colons. This coincided with elevated levels of the proinflammatory cytokines IL-1, IL-4, IL-5, and IL-13, and suggests that APN may at some level regulate autoimmunity.

Taken together, at the level of the two major adipocytokines leptin and APN, they have an immune-regulatory role. High serum leptin and low serum APN coexist during obesity and promote an anti-inflammatory response, through the induction IL-6 and TNF-α, and reduced IL-10. At the immune level, leptin decreases the number of Treg cells [130], which are important in ameliorating intestinal inflammation, and reduced APN is associated with a B cell response and STAT3 activation [129]. Both leptin and APN are elevated in the fat deposits in the gut and are associated with inflammation, but further in-depth mechanistic studies are required to assess their role from this tissue compartment.

Given from the above discussion that a HFD can limit Treg activity and promote ER stress and further potentiate inflammation, a possible scenario is that increased leptin and low APN further reinforce and amplify the inflammatory response. This we have illustrated in Fig. 1. Considering as well the genetic mutations linked with IBD, it is then conceivable that certain carriers are more susceptible or possibly even resistant to disregulated adipocytokine levels. Moreover, given the metabolic roles of these and other adipocytokines that we have not here discussed, for instance their actions in energy sensing pathways, their influence on the microbiome needs to be additionally evaluated. Thus, further studies are required to delineate these associations.

7. Conclusions and the future direction of research

The adipose tissue is a very active organ and as it expands due to a disequilibrium between energy intake and energy expenditure, and the secretion of adipocytokines is disturbed. These differences correspond with several diseases, such as the metabolic syndrome, increased cardiovascular risk, insulin resistance and certain cancers. Population studies have not been convincing in providing direct linkages between IBD and obesity. However, in murine models, the incorporation of genetic mutations found in human IBD patients, and the digestion of a high fat diet can potentiate colonic inflammation, an unfolded protein response, colonic permeability, and promote dysbiosis (Table 2). Another avenue through which colonic inflammation can become dysregulated is through altered systemic levels of adipocytokines. How adipocytokines affect the colon and IBD progression in the presence of other mutations presented here remains to be determined. It is likely that adipokine interactions in IBD is patient specific, and therapeutic responses will have to be developed to incorporate this diversity.

Supported by: Queensland Cancer Council Project Grant (APP1123436, LH) and James Cook Development Grant (94066) 2016-17 (LH).

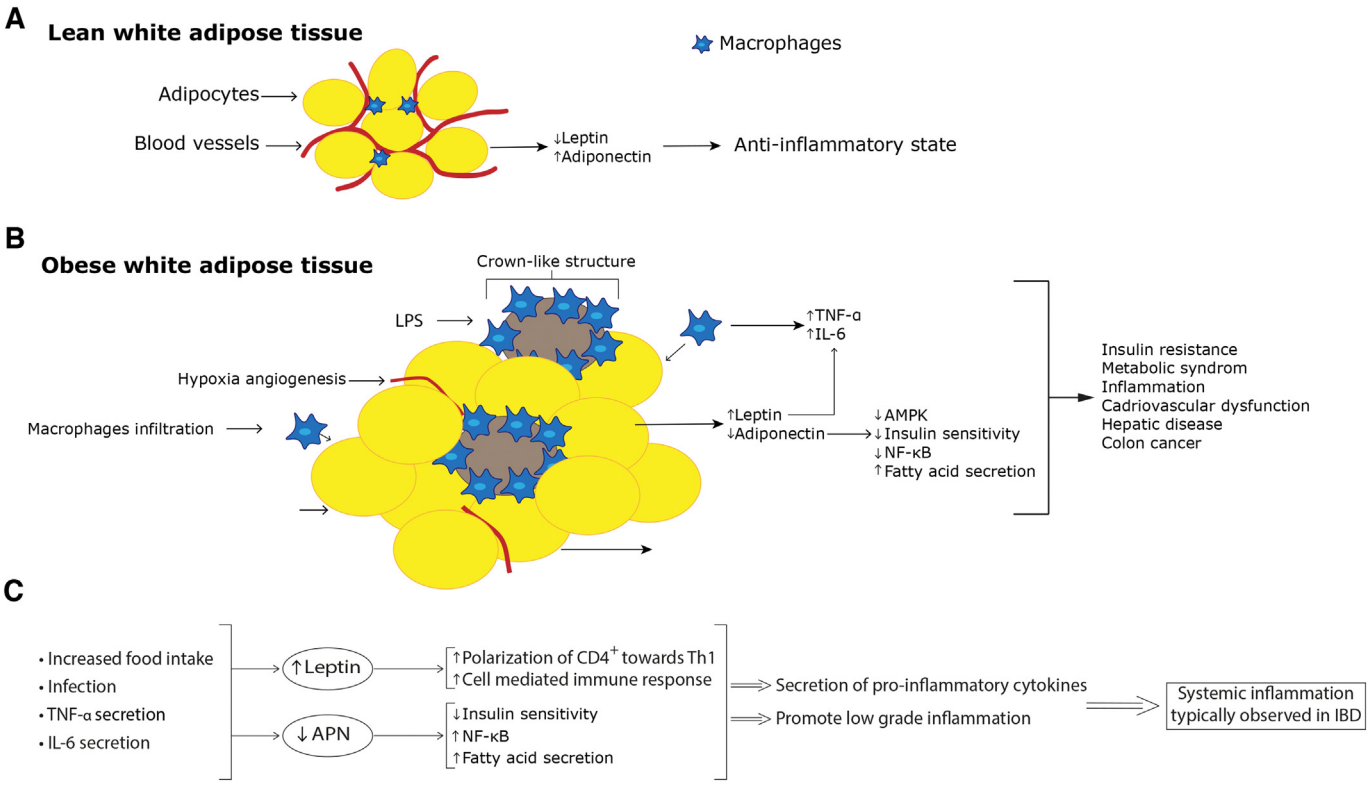

Fig. 1. Adiposity promotes larger and inflammatory adipocytes. A, In the normal fasting state low levels of serum leptin and high levels of serum adiponectin promote an anti-inflammatory state. B, During obesity adipocytes undergo hypertrophy and reach a threshold size, and hyperplasia is promoted and pre-adipocytes differentiate into mature adipocytes. Expansion of the adipose results in poor vascularisation and apoptosis, which promotes hypoxia and subsequent angiogenesis. Infiltrating macrophages form crown-like structures around dead cells, and release inflammatory cytokines, such as TNF-α and IL-6. Inflammatory ligands like lipopolysaccharide (LPS), activate Toll-like receptors (TLR) and activate the NF-κB pathway to reinforce inflammatory cytokine production. The WAT secretion of leptin and adiponectin becomes dysregulated and affects insulin resistance, the metabolic syndrome, inflammation, cardiovascular dysfunction and hepatic disease. C, summation of the inflammatory and metabolic effects of leptin and adiponectin in IBD.

Table 2
Studies linking obesity with colitis in murine models.

Publications	Mouse	Research conditions	Symptoms
[86]	Male wild-type C57BL/6	HFD Acute DSS	• Shorter colon • Diarrhoea • Bleeding • Weight loss • Crypts damage • Immune cell infiltration • Epithelial loss
[85]	Male wild-type C57BL/6	HFD Chronic DSS	• Shorter colons • Weight loss • Mucus layer greatly altered • Crypts damage • Ulcers
[129]	Male wild-type C57B/6 Male APN-KO C57B/6	Normal diet Acute DSS	• Colon crypts damaged • Shorter colon • Immune cell infiltration • Weight loss • Bleeding • Inflammatory cytokines upregulation
[62]	Male Winnie C57BL/6 background	Normal diet Acute DSS	Spontaneous • Neutrophil infiltration • Goblet cell loss • Crypts abscesses • Epithelial erosion DSS • Immune cell infiltration • Rectal bleeding • Loss of epithelium
[89]	Male wild-type C57BL/6 Male & female Winnie C57BL/6 background	HFD	• Enhances oxidative stress • Enhanced ER stress in the intestinal epithelium cells • Disorders in the protective mucus layer • Inflammation
[126]	Female *ob/ob* C57BL/6J Female wild-type C57BL/6J	Normal diet Acute & chronic DSS	• Obese • Protected against colitis

Transparency document

The Transparency document associated with this article can be found, in online version.

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