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Adipokines and the role of visceral adipose tissue in inflammatory bowel disease

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Abstract

Recently, adipocytes have been recognized as actively participating in local and systemic immune responses via the secretion of peptides detectable in relevant levels in the systemic circulation, the so-called "adipo(cyto)kines". Multiple studies appearing within the last 10-15 years have focused on the possible impact of adipose tissue depots on inflammatory bowel disease (IBD). Consequently, various hypotheses regarding the role of different adipokines in inflammatory diseases in general and in intestinal inflammatory processes in particular have been developed and have been further refined in recent years. After a focused summary of the data reported concerning the impact of visceral adipose tissue on IBD, such as Crohn's disease and ulcerative colitis, our review focuses on recent developments indicating that adipocytes as part of the innate immune system actively participate in antimicrobial host defenses in the context of intestinal bacterial translocation, which are of utmost importance for the homeostasis of the whole organism. Modulators of adipose tissue function and regulators of adipokine secretion, as well as modifiers of adipocytic pattern recognition molecules, might represent future potential drug targets in IBD.

Keywords Inflammatory bowel disease, Crohn's disease, ulcerative colitis, adipose tissue, adipokines, leptin, adiponectin, innate immunity

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Introduction

Recently, adipocytes have been recognized to actively participate in systemic immune responses via the secretion of peptides detectable in relevant levels in the systemic circulation, the so-called "adipo(cyto)kines" [1-3]. Multiple original studies and review articles appearing within the last 10-15 years have focused on the possible impact of adipose tissue depots on inflammatory bowel disease (IBD). A recent search of the PubMed database (in April 2016) using the search terms *"inflammatory bowel disease AND fat (adipose) tissue"* resulted in 316 items. Publications in this field are constantly growing in number and increasingly concentrate on adipokines. The search terms *"inflammatory bowel disease AND adipokines"* returned 132 publications. Leptin is the most prominent adipokine in the field of IBD research, as 83 of these 132 publications were related to leptin, followed by adiponectin, resistin, visfatin and others. Because of the growing body of data, the number of review articles in this field is also increasing, with a total number of 45 review articles returned when the search terms *"review AND inflammatory bowel disease AND adipose tissue"* were used. Among these 45 articles, 15 focus on adipokines/secreted factors, 9 on mesenchymal stem cells/fibrosis, 4 on obesity/muscle/exercise, 3 on peroxisome proliferator-activated receptor γ (PPARγ), 3 on the innate immunity of adipocytes, 2 on metabolism/fatty acids, 2 on neurotransmitters/neuropeptides, and 7 on other or mixed topics.

Various hypotheses regarding the role of different adipokines in inflammatory diseases in general and in intestinal inflammatory processes in particular have been developed and have been further refined in recent years. It is not the intent of this review to reiterate these developments in detail. Rather, after a focused summary of the data reported on the impact of visceral adipose tissue (VAT) on IBD, such as Crohn's disease and ulcerative colitis, our manuscript will focus on recent developments indicating that, in the context of intestinal bacterial translocation, adipocytes actively participate as part of the innate immune system in antimicrobial host defenses, which are of utmost importance for the homeostasis of the whole organism.

Interestingly, inflammatory visceral fat hypertrophy (also named "creeping fat") is indicative for Crohn's disease to an

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extent that it has been proposed as a useful diagnostic marker in the differential diagnosis of IBD from other intestinal inflammations such as intestinal tuberculosis [4]. In computed tomography scans, the increase in submucosal fat in patients with Crohn's disease of longer duration leads to a characteristic "fat halo sign" [5].

Early studies described an inflammatory reaction of hypertrophic mesenteric adipose tissue (MAT) in patients with Crohn's disease, characterized by increased concentrations of PPARγ and tumor necrosis factor α (TNFα) within the mesenteric fat depot [6]. Similar results were found in experimental 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis in mice [7], while infliximab treatment restored MAT PPARγ expression to baseline in these mice [8]. Interestingly, the angiotensin II type 1 receptor blocker and PPARγ agonist telmisartan ameliorated spontaneous colitis in interleukin-10-deficient (IL-$10^{-/-}$) mice, restoring VAT morphology and adipokine secretion to a non-colitic phenotype [9]. Notably, mice deficient in Toll-like receptor 9 (TLR9) signaling ($TLR9^{-/-}$), resistant to chronic dextran sulfate sodium (DSS)-induced colitis, exhibit an altered adipokine expression profile in VAT compared to wild-type mice [10].

Remarkably, PPARγ is the key transcriptional regulator in the terminal differentiation of adipocytes from mesenchymal stem cells [11,12]. These data imply an intricate relationship between intestinal inflammation and adjacent VAT, more than merely being a passive "bystander".

Obesity and IBD: bystanders, mutual friends, or enemies?

Generally, obesity has been postulated to contribute to the onset and progression of various autoimmune diseases in humans [13]. While earlier reports indicated that the prevalence of obesity was lower in patients suffering from IBD than in the general population [14,15], the overall incidence of obesity in these patients has recently been increasing and is currently estimated to be around 25-30%, similar to the rate in the general population [16,17]. Interestingly, bariatric surgery has been observed to improve intestinal inflammation in patients with IBD [18], although other reports caution against a potentially deleterious effect [19,20]. While earlier reports hinted at a potentially worse disease course in obese as compared to normal-weight IBD patients [15,21], other authors found less severe disease in obese patients [22]. Diet-induced obesity worsens TNBS-induced experimental colitis in mice [23] as well as spontaneous intestinal inflammation in multidrug resistance protein 1a deficient mice [24]. In IBD patients, however, the large "IBD in EPIC Study", which included more than 300,000 participants, found no association between IBD and obesity, measured by body mass index (BMI) [25]. It should be noted that BMI is only a crude index of obesity, and this may be partly responsible for the lack of association in this large study. In summary, the impact of obesity on IBD remains to be clarified.

Do drugs that induce weight loss in obese patients [26,27] impact on the incidence, prevalence and/or clinical course of IBD? No data in this regard are available on sympathomimetic drugs approved for short-term use (amfepramone, benzphetamine, diethylpropion, phendimetrazine, phentermine, ephedrine, caffeine). Interestingly, bupropion, an antidepressant used in the pharmacotherapy of obesity, has shown beneficial effects on intestinal ischemia/reperfusion injury in rats [28], while the opioid antagonist naltrexone effectively reduced intestinal inflammation in human Crohn's disease, as well as in rodent models of colitis [29-31]. However, these observations were mostly short-term effects, while the weight-lowering effects of these compounds are expected with longer-term use. Thus, reduced intestinal inflammation in these models is not likely to be causally linked to weight loss or reduced adipocyte numbers.

For long-term treatment of obesity aimed at inducing weight loss, orlistat, lorcaserin and the combination phentermine/topiramate have been approved [26,27]; however, no data are available regarding the impact of these compounds on IBD. Interestingly, glucagon-like peptide-2 (GLP-2) had beneficial effects in rodent enteritis models [32,33], and inhibition of the GLP-diminishing enzyme dipeptidyl peptidase 4 had beneficial effects in acute DSS-induced colitis in mice [34]. No data are available on GLP-1-analogs in autoimmune intestinal inflammation.

Importantly, metformin has been demonstrated to inhibit TNFα-induced proinflammatory cytokine induction in colonic epithelial cells via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway inhibition *in vitro* [35]. Metformin treatment, via signal transducer and activator of transcription 3/IL-17 inhibition, ameliorated murine acute DSS-induced colitis as well as chronic colitis in IL-$10^{-/-}$ mice [35,36]. Additionally, metformin treatment reduced colitis-associated tumorigenesis in rats and mice [35,37]. However, no data are available on metformin treatment in patients suffering from IBD.

There is a wealth of data proving the beneficial effect of PPARγ agonists (thiazolidinediones, "glitazones") in IBD. PPARγ receptors were originally described in adipose tissue, and agonistic compounds have long been used as insulin-sensitizing, antidiabetic agents in patients [38,39]. Observational studies did not find a significant reduction in ulcerative colitis flares in patients receiving thiazolidinediones as compared to other oral antidiabetic drugs [40]; however, the systemic and local administration of rosiglitazone had beneficial effects in ulcerative colitis patients [41-43].

In summary, several insulin-sensitizing and weight-lowering drugs have pleiotropic, beneficial effects on autoimmune intestinal inflammation (Table 1). However, data in the literature on the impact of obesity in general on IBD are contradictory. A closer look at possible underlying mechanisms might shed some light on these discrepancies. How adipocytes, as key players in obesity, might impact on the intestine remains to be elucidated.

Table 1 Summary of studies investigating the efficacy of antidiabetic and weight-lowering drugs in intestinal inflammation

Drug	Organism	Model	Effect on colitis	Net effect	Reference
Metformin	Mice	Acute DSS colitis	↓	↓	[35]
Metformin	Mice	Spontaneous colitis in IL-10$^{-/-}$ mice	↓		[35]
Metformin	Mice	Acute DSS colitis	↓		[36]
Rosiglitazone	Human	Ulcerative colitis	↓	↓	[41]
Rosiglitazone	Human	Ulcerative colitis	↓		[42]
Rosiglitazone enema	Human	Ulcerative colitis	↓		[43]
Rosiglitazone	Rat	Acute DSS colitis	↓		[154,155]
Rosiglitazone	Rat	Acute DSS colitis	↓		[156]
Rosiglitazone	Rat	Acute TNBS colitis	↓		[157]
Rosiglitazone	Rat	Acute TNBS colitis	↓		[158]
Rosiglitazone	Rat	Chronic TNBS colitis	↓		[159]
Rosiglitazone	Mice	Acute DSS colitis	↑		[160]
Rosiglitazone	Mice	Acute DSS colitis	↓		[161]
Rosiglitazone	Mice	Acute DSS colitis	↓		[162]
Rosiglitazone	Mice	Acute TNBS colitis	↓		[163]
Rosiglitazone	Mice	Acute TNBS colitis	↓		[164]
Rosiglitazone	Mice	Spontaneous colitis in IL-10$^{-/-}$ mice	↓		[165]
Pioglitazone	Mice	Acute DSS colitis	↓		[166]
Pioglitazone	Mice	Acute DSS colitis	↓		[167]
Pioglitazone	Mice	Acute DSS colitis	↓		[162]
Netoglitazone	Mice	Acute DSS colitis	↓		[166]
Troglitazone	Rat	Acute DSS colitis	↓		[154,155]
Troglitazone	Rat	Acute DSS colitis	↓		[168]
Troglitazone	Mice	Acute DSS colitis	↓		[162]
Bupropion	Rat	Intestinal ischemia/reperfusion injury	↓	↓	[28]
Naltrexone	Human	Crohn's disease	↓	↓	[29]
Naltrexone	Human	Crohn's disease	↓		[31]
Naltrexone	Mice	Acute DSS colitis	↓		[30]
GLP-2	HLA-B27 rats	Spontaneous small bowel enteritis	↓	↓	[33]
GLP-2	Mice	Indomethacin-induced small bowel enteritis	↓		[32]
DPP-IV-Inhibitors	Mice	Acute DSS colitis	↓	↓	[34]

Effect on colitis: ↓ amelioration; ↑ aggravation

GLP-2, glucagon-like peptide-2; DPP-IV, dipeptidyl peptidase 4; DSS, dextran sulfate sodium; TNBS, 2,4,6-trinitrobenzenesulfonic acid; IL-10$^{-/-}$ mice, interleukin-10 deficient mice; HLA-B27 rats, animals derived from Fisher (F344) rat zygotes microinjected with human HLA-B27 and beta2-microglobulin genes inducing spontaneous chronic gastrointestinal inflammation

Data are organized according to pharmaceutical substance groups (column 1), and within groups according to model organism (human, rat, mice – column 2) followed by model of intestinal inflammation (column 3)

Adipocytes in IBD: is it all about adipokines?

Historically seen as passive bystanders, adipocytes have increasingly been recognized as active participants in a variety of physiological reactions, including the immune system, via the expression and secretion of multiple hormone-like factors with auto- and paracrine effects, the so-called adipokines. Various different adipokines with pleiotropic roles have been described in this regard, many of which are found in significant concentrations in the systemic circulation [1-3,44-46]. These adipokines show correlations with the activity of a variety of autoimmune as well as infectious diseases [13,47]. Given the ill-defined role of obesity in IBD, it was an obvious necessity to investigate the role of defined adipokines and the potential diagnostic and pathophysiological value of systemic serum levels of adipokines in patients suffering from IBD, and to

correlate these findings with observations made in different mouse models of (autoimmune) intestinal inflammation.

One of the first adipokines to be investigated in relation to intestinal inflammation was leptin, in 2002. Based on the observation that leptin-deficient animals, as well as humans, exhibit defective T-cell-function, Siegmund *et al* sought to determine whether experimentally induced colitis (DSS- and TNBS-induced colitis models) was affected in leptin-deficient (ob/ob) mice. They found that intestinal inflammation in both experimentally induced colitis models was significantly attenuated in ob/ob mice [48]. These results were mirrored by a markedly reduced inflammatory activity in oxazolone-induced colitis in mice and in a mouse model of infectious diarrhea (*Clostridium difficile* toxin A-induced enteritis) [49,50]. Similar observations were made regarding the DSS-induced colitis model, the *Clostridium difficile* toxin A-induced enteritis model, and the infectious *Clostridium difficile*-induced colitis model in both leptin-receptor-deficient (db/db) mice [50-52] and leptin receptor-mutant mice [52]. On the other hand, intrarectal leptin administration induced mucosal inflammation in mice [53]. Pathophysiologically, leptin proved to be an important inducer of various proinflammatory cytokines and played a regulatory role in T cell polarization [49].

Remarkably, no differences were demonstrated in the $CD4^+CD45RB^{high}$ transfer model of colitis [54,55] when cells from ob/ob mice were transferred, indicating that leptin's impact on colitis is not mediated by T cell secretion. Rather, when $CD4^+CD45RB^{high}$ cells of db/db mice were used in this transfer model of colitis, the receptor animals showed a delayed colitis onset, indicating that leptin does act on T cells under these circumstances. It is noteworthy that no differences were noted in the course of spontaneous colitis in ob/ob x IL-$10^{-/-}$ mice compared to wild-type (wt)/wt x IL-$10^{-/-}$ mice, indicating that leptin does not impact on intestinal inflammation in this model. Table 2 summarizes the results of experimental animal studies that investigated leptin's role in different models of intestinal inflammation.

Interestingly, systemic leptin serum levels in mice seem to be reduced in different models of colitis [56-59], while other groups found increased versus unchanged serum levels in other colitis models in rats [8,60]. Studies investigating systemic leptin serum levels in patients suffering from IBD reported contradictory results, summarized in Table 4; while some groups found increased leptin concentrations in the systemic circulation in active IBD [61,62], others reported reduced [63-66] or unchanged systemic leptin levels [65,67-70], in part depending on the disease subgroup (Crohn's disease versus ulcerative colitis). However, separate disease subgroups and different patient cohorts were not sufficient to explain the varying results. Another potential source of heterogeneity between studies is the different treatment status of the IBD patients who were included; however, data from truly treatment naïve patients are sparse.

It has been demonstrated that adipocytes are the main contributors to systemic leptin serum levels [71,72]. However, keeping in mind that data in the literature on the impact of obesity in general on IBD are contradictory, generalized fat hypertrophy might not completely reflect the changes relevant

Table 2 Summary of experimental animal studies investigating the role of leptin and leptin receptor signaling in intestinal inflammation

Genotype	Organism	Model	Effect on colitis	Net effect	Reference
ob/ob	Mouse	Acute DSS colitis	↓	↓	[48]
ob/ob	Mouse	Chronic DSS colitis	↓		[48]
ob/ob	Mouse	TNBS colitis	↓		[48]
ob/ob	Mouse	Oxazolone-induced colitis	↓		[49]
ob/ob	Mouse	*Clostridium difficile* toxin A-induced enteritis	↓		[50]
ob/ob	Mouse	$CD4^+CD45RB^{high}$ transfer model of colitis	↔		[54]
ob/ob	Mouse	IL-$10^{-/-}$	↔		[55]
db/db	Mouse	Acute DSS colitis	↓	↓	[51]
db/db	Mouse	$CD4^+CD45RB^{high}$ transfer model of colitis	↓		[169]
db/db	Mouse	*Clostridium difficile* toxin A-induced enteritis	↓		[50]
db/db	Mouse	*Clostridium difficile*-induced colitis	↓		[52]
Leptin receptor (LEPR) gene mutant for Y1138 (s/s mice)	Mouse	Acute DSS colitis	(↓)	↓	[51]
Leptin receptor (LEPR) gene mutant for Y1138 (s/s mice)	Mouse	Clostridium difficile-induced colitis	↓		[52]
wt/wt	Mouse	Intrarectal leptin administration	↑	↑	[53]

Effect on colitis: ↓ amelioration; ↑ aggravation; ↔ no change

ob/ob mice, leptin deficient mice; db/db mice, leptin-receptor deficient mice; wt/wt mice, wild-type mice; DSS, dextran sulfate sodium; TNBS, 2,4,6-trinitrobenzenesulfonic acid; $CD4^+CD45RB^{high}$ transfer model of colitis, adaptive transfer of $CD4^+CD45RB^{high}$ T cells (naïve T cells) from healthy donor mice into syngeneic recipients that lack T and B cells, inducing pancolitis and small bowel inflammation; IL-$10^{-/-}$ mice, interleukin-10 deficient mice

Data are organized according to genotypes (column 1), and within genotypes according to the model of intestinal inflammation (column 3)

Table 3 Summary of experimental animal studies investigating the role of adiponectin in intestinal inflammation

Genotype	Organism	Model	Effect on colitis	Net effect	Reference
APN$^{-/-}$	Mouse	Acute DSS colitis	↑	??	[78]
APN$^{-/-}$	Mouse	Acute DSS colitis	↑		[79]
APN$^{-/-}$	Mouse	Acute DSS colitis	↑		[80]
APN$^{-/-}$	Mouse	Acute DSS colitis	↓		[82]
APN$^{-/-}$	Mouse	Acute DSS colitis	↓		[81]
APN$^{-/-}$	Mouse	TNBS colitis	↔	??	[78]
APN$^{-/-}$	Mouse	TNBS colitis	↓		[82]
APN$^{-/-}$	Mouse	Irradiation-induced damage	↔	↔	[83]
APN$^{-/-}$	Mouse	CD4^{+}CD45RB^{high} induced colitis	↔	↔	[84]
APN$^{-/-}$	Mouse	IL-10$^{-/-}$	↔	↔	[85]

Effect on colitis: ↓ amelioration; ↑ aggravation; ↔ no change; ?? data contradictory

APN$^{-/-}$, adiponectin deficient mice; DSS, dextran sulfate sodium; TNBS, 2,4,6-trinitrobenzenesulfonic acid; CD4^{+}CD45RB^{high} transfer model of colitis, adaptive transfer of CD4^{+}CD45RB^{high} T cells (naïve T cells) from healthy wild-type mice into syngeneic recipients that lack T and B cells, inducing pancolitis and small bowel inflammation; IL-10$^{-/-}$ mice, interleukin-10 deficient mice

Data are organized according to genotypes (column 1), and within genotypes according to the model of intestinal inflammation (column 3)

in IBD in humans. Rather, the observed localized hypertrophy of fat tissue, particularly MAT, which is accompanied by proinflammatory changes within these fat depots [6], hints at possible paracrine effects of adipokines produced and secreted by mesenteric adipocytes. Remarkably, all studies investigating the leptin secretion/mRNA induction in MAT/VAT in IBD patients found unequivocally increased levels [23,73-75]. These results are mirrored by studies in MAT/VAT in rodent models of colitis [7,10,76]. In summary, leptin produced by MAT/VAT is upregulated and seems to act in a paracrine manner on the intestine as a proinflammatory mediator in patients suffering from IBD as well as in rodent models of colitis.

One of the first proteins demonstrated to be synthesized and secreted in large quantities almost exclusively by adipocytes, and as such one of the first "adipokines", was adipocyte complement-related protein of 30 kDa (Acrp30), later termed "adiponectin" in 1995 [77]. Structurally, adiponectin has a globular head domain similar to complement factor C1q, as well as a collagen-like domain, and forms different higher-molecular secondary and tertiary structures. It was demonstrated to be detectable in significant quantities in the systemic circulation [77].

Studies by Nishihara and colleagues in 2006 demonstrated that acute DSS-induced colitis was significantly aggravated in adiponectin-deficient (APN$^{-/-}$) mice, indicating that adiponectin had a protective effects on colitis in this model [78]. Other studies were able to reproduce these results [79,80]. Surprisingly, Fayad *et al* reported in 2007 that both acute DSS-induced colitis and acute TNBS-induced colitis were ameliorated in APN$^{-/-}$ mice [81,82], whereas Nishihara had found that TNBS-induced colitis remained unchanged in APN$^{-/-}$ mice [78]. Although differences in the concentration of DSS/TNBS chosen in these models have been held accountable for some of the observed inconsistencies, the impact of adiponectin on acute intestinal inflammation in mouse models remains elusive. No impact of adiponectin deficiency could be demonstrated on acute irradiation-induced small-intestinal damage [83], nor on mouse models of chronic autoimmune intestinal inflammation (CD4^{+}CD45RB^{high} induced colitis model, APN$^{-/-}$ x IL-10$^{-/-}$) [84,85]. Table 3 summarizes the results of experimental animal studies that investigated adiponectin's role in different models of intestinal inflammation.

Furthermore, the data regarding systemic serum levels of adiponectin in human IBD are also quite heterogeneous (Table 4). While some authors reported systemic serum levels to be unchanged in active Crohn's disease and ulcerative colitis [63,65], others found reduced [67,68] or increased [64] adiponectin concentrations in the systemic circulation. Remarkably, as with the observations concerning leptin discussed above, all studies investigating the adiponectin secretion/mRNA induction in MAT/VAT in IBD patients found unequivocally increased levels [23,73,74,86]. However, in contrast to the data for leptin in animal models, these results were not completely mirrored by rodent models of colitis, where the data relating to MAT/VAT are contradictory (adiponectin levels decreased [87] versus increased [7,76]). These observations do implicate adiponectin, like leptin, as an important local mediator produced by mesenteric/visceral adipocytes and potentially impacting on the intestine in a paracrine manner in patients suffering from IBD, as well as in rodent models of colitis. However, as opposed to the clearly proinflammatory role of leptin, the exact impact of adiponectin on inflammation (pro-/anti-inflammatory) remains elusive.

Multiple other adipokines have been investigated in human autoimmune intestinal inflammation and in various rodent models of colitis. For example, systemic chemerin levels are elevated in experimental DSS-induced colitis in mice and intraperitoneal chemerin treatment exacerbates the disease, while treatment with anti-chemerin antibodies ameliorates colitis in this model [88,89]. However, data from serum samples of patients with Crohn's disease or ulcerative colitis are contradictory [63,90]. Systemic resistin levels seem to be increased in patients with active IBD [63,64,67,91]; however, studies specifically targeting resistin expression/secretion in VAT in these patients found conflicting results [23,74]. Visfatin serum levels were increased in IBD patients [63,67,92], but this result could not be reproduced in rodent models of colitis [10,93]. The new adipokine C1q/TNF-related protein-3 (CTRP-3) is synthesized and secreted by MAT and ameliorates lipopolysaccharide (LPS)-induced IL-8 secretion, while reducing the basal expression of transforming growth factor β, connective tissue growth factor and collagen I in Crohn's disease colonic lamina propria fibroblasts [94]. However, no difference was observed in VAT CTRP-3 mRNA expression between chronic DSS-induced colitis in mice compared to control mice [10]. Finally, there are reports that systemic

Table 4 Summary of observational studies investigating visceral adipose tissue adipokine expression, secretion and/or systemic levels in autoimmune intestinal inflammation

Adipokine	Organism	Sample	Disease/Model	Effect	Net effect	Reference
Adiponectin	Human	Serum	UC active/CD active	↔	??	[63]
			UC/CD active+inactive	↓		[67]
			UC/CD active+inactive	↑ (sign. for UC)		[64]
			CD active	↓		[68]
	Human/children	Serum	UC active/CD active	↔		[65]
Chemerin	Human		UC active/CD active	↔	??	[63]
			UC/CD active+inactive	↑		[90]
Ghrelin	Human		UC/CD active+inactive	↑	↑	[64]
Leptin	Human	Serum	UC active/CD active	↓	??	[63]
			UC active	↑		[61]
			UC/CD active+inactive	↔		[67]
			UC/CD active+inactive	↓ (sign. for UC)		[64]
			UC active	↑		[62]
			CD active	↔		[68]
			CD active+inactive	↔		[69]
	Human/children	Serum	UC active	↓		[65]
			CD active	↔		[65]
			UC active+CD active	↓		[66]
			CD/UC active+inactive	↔		[70]
Omentin-1	Human	Serum	UC active/CD active	↓	↓	[95]
RBP-4	Human	Serum	UC/CD active+inactive	↑	↑	[67]
Resistin	Human	Serum	UC active/CD active	↑	↑	[63]
			UC active/CD active	↑		[67]
			UC active/CD active	↑		[91]
			UC/CD active+inactive	↑		[64]
Visfatin	Human	Serum	UC active	↑	↑	[92]
			UC active/CD active	↑		[63]
			UC active	↑		[67]
Adiponectin	Human	VAT secretion	UC active/CD active	↑	↑	[23]
			UC active/CD active	↑		[73]
		MAT secretion	CD active	↑		[86]
			CD active	↑		[74]
		MAT mRNA	CD active	↑		[86]
Leptin	Human	VAT secretion	UC active	↑	↑	[23]
			CD active	↔		[23]
			UC active/CD active	↑		[73]
		MAT secretion	CD active	↑		[74]
		MAT mRNA	UC/CD active+inactive	↑		[75]
Resistin	Human	VAT secretion	UC active	↔	??	[23]
			CD active	↓		[23]
		MAT secretion	CD active	↑		[74]

(*Contd...*)

Table 4 (*Continued*)

Adipokine	Organism	Sample	Disease/Model	Effect	Net effect	Reference
Leptin	Mouse	Serum	Colitis in Gαi2$^{-/-}$ mice	↓	↓	[56]
			DSS-AC	↓		[57]
			DSS-AC	↓		[58]
			IL-2$^{-/-}$ spont. colitis	↓		[59]
Adiponectin	Mouse	MAT mRNA	DSS-AC, DNBS	↓	↓	[87]
CTRP-3	Mouse	VAT mRNA	DSS-CC	↔	↔	[10]
Leptin	Mouse	MAT mRNA	DSS-AC, DNBS	↓	??	[87]
		VAT mRNA	DSS-CC	↑		[10]
Visfatin	Mouse	VAT mRNA	DSS-CC	↔	↔	[10]
Adiponectin	Rat	Serum	TNBS	↔	↔	[8]
Leptin	Rat	Serum	TNBS	↔	??	[8]
			TNBS	↑		[60]
Resistin	Rat	Serum	TNBS	↔	↔	[8]
Visfatin	Rat	Serum	Acetic-acid ind. colitis	↓	↓	[93]
Adiponectin	Rat	PAT secretion	TNBS	↑	↑	[76]
			TNBS	↑		[7]
		MAT secretion	TNBS	↔		[7]
Leptin	rat	PAT secretion	TNBS	↑		[76]
			TNBS	↑		[7]
		MAT secretion	TNBS	↔		[7]

Change during colitis: ↓ reduction; ↑ increase; ↔ no change; ?? data contradictory

RBP-4, retinol binding protein 4; CTRP-3, C1q/tumor necrosis factor-related protein-3; VAT, visceral adipose tissue; MAT, mesenteric adipose tissue; PAT, perinodal adipose tissue surrounding mesenteric lymph nodes; UC, ulcerative colitis; CD, Crohn's disease; Gαi2$^{-/-}$ mice, mice with a targeted mutation in the gene for the G protein αi2 subunit causing an inflammatory bowel disorder resembling human ulcerative colitis; IL-2$^{-/-}$ mice, interleukin-2 deficient mice; DSS-AC, acute dextran sulfate sodium-induced colitis model; DSS-CC, chronic dextran sulfate sodium-induced colitis model; DNBS, 2,4-dinitrobenzene sulfonic acid-induced colitis model; TNBS, 2,4,6-trinitrobenzenesulfonic acid-induced colitis model; spont., spontaneous; ind., induced; sign., significant

Data are organized according to organism (human, human/children, mouse, rat–column 2). Within organism groups, data are organized according to sample type (serum, VAT/MAT secretion/mRNA–column 3) followed by adipokines (column 1)

serum levels of retinol-binding protein 4 [67] and ghrelin [64] are increased, while omentin-1 [95] is reduced in IBD patients. Table 4 summarizes the observational studies reported to date that investigated VAT expression, secretion and systemic adipokine levels in human IBD as well as in rodent models of intestinal inflammation.

Abdominal fat depots in IBD

Interestingly, diet-induced increased VAT mass in mice worsens the course of experimental TNBS-induced colitis, possibly via reduced intestinal epithelial cell adiponectin-receptor 1 expression [23]. A higher visceral-to-subcutaneous fat ratio is associated with and predictive for postoperative surgical morbidity in Crohn's disease patients, whereas BMI is not [96,97]. In patients with Crohn's disease, a higher visceral fat area is predictive of postoperative recurrence [98] and is associated with strictures and fistulas [99]. Pediatric IBD patients had 33% more VAT volume than age- and BMI-matched controls, and in these patients VAT was associated with complications of the disease course, for example fistulas, fibrosis and need for hospitalization [100]. In contrast, however, other studies found that an increased subcutaneous-to-visceral fat volume was predictive for postoperative complications after bowel resection in Crohn's disease [101].

It should be noted that earlier reports found increased proinflammatory cytokine expression in MAT during TNBS-induced colonic inflammation in mice, which seemed to be mediated via increased substance P-induced neurokinin 1 receptor expression [102]. Studies in human IBD revealed that VAT in Crohn's disease patients had a more proinflammatory gene expression profile as compared to ulcerative colitis [103]. Consequently, mesenteric fat has been proposed as a key player in Crohn's disease [104]. Hypertrophic VAT adjacent to inflammatory lesions in Crohn's disease patients exhibits proinflammatory gene expression; however, even VAT at sites distant from inflammatory lesions shows upregulated expression of genes involved in inflammation and immunity, similar to the changes observed in the VAT of obese patients [105]. In mice, both a high-fat diet and DSS-induced colitis induce similar

inflammatory changes in VAT [106]. Interestingly, infliximab therapy in Crohn's disease patients leads to an 18% increase in total abdominal fat, although the metabolic profile of these patients (glycemia, lipid profile) does not worsen [107]. Since VAT has been shown to be a key contributor to metabolic disturbances in obese patients [108-110], these results hint at potentially different reactions of VAT in autoimmune intestinal inflammation as opposed to the proinflammatory changes within the adipose tissue seen in obese patients.

Importantly, studies in human IBD revealed that VAT in Crohn's disease with a proinflammatory gene expression profile is significantly more colonized by intestinal commensal bacteria of type *Enterococcus faecalis* [103]. In Crohn's disease, as opposed to ulcerative colitis, translocation of intestinal bacteria to mesenteric fat depots has been demonstrated, leading to increased C-reactive protein secretion in systemically relevant levels in these adipocytes [111]. Notably, ovalbumin peptides translocate to MAT in healthy mice, which is not increased in experimental DSS-induced colitis. However, viable translocation of bacteria to MAT does not occur in healthy animals, but is increased in chronic DSS-induced colitis [112].

The importance of an intact intestinal barrier function for (intestinal) homeostasis has long been recognized, as has the key importance of intestinal (commensal) microbiota in the development of intestinal bowel diseases [113-116]. Together with accumulating data indicating innate immune responses in adipocytes [117-119], VAT is increasingly recognized as a key player in the maintenance of homeostasis. MAT from Crohn's disease patients, as well as from mice suffering from TNBS-induced colitis, shows increased expression levels of PPARγ, farnesoid X receptor, leptin and adiponectin, which can be abrogated by probiotic treatment that reduces inflammatory activity [120]. Importantly, even without an inflammatory stimulus, VAT proinflammatory reactions are of physiological relevance in basal (intestinal) homeostasis, since an adipocyte-specific reduction of proinflammatory signaling in mice (aP2-dnTNF, a mouse model expressing a dominant-negative version of TNFα under the control of the ap2-promoter; aP2-RID, a mouse model expressing the adenoviral RIDα/β protein complex, which inhibits a number of proinflammatory signaling pathways under the control of the ap2-promoter; and TRE-IκBα, a mouse model expressing a mutated functional human IκBα, an inhibitor of the NF-κB pathway, under the control of a tet-responsive element) leads to increased lipid accumulation, glucose intolerance and systemic inflammation associated with impaired intestinal barrier function via impaired "healthy" adipose tissue expansion and remodeling [121]. VAT and leptin increase intestinal barrier permeability in rats *in vivo* without obvious inflammatory reactions in the intestine, and in colonic epithelial cells in co-culture experiments *in vitro* via a RhoA-ROCK-dependent pathway (RhoA, small GTPase protein of the Rho family, associated with cytoskeleton regulation; and ROCK, rho-associated, coiled-coil containing protein kinase) [122]. Other studies demonstrated that increased VAT is also associated with increased intestinal barrier permeability in healthy women [123].

In summary, accumulating data indicate that, rather than a general increase in fat, local fat depots, particularly the visceral fat depot, actively participate in intestinal inflammatory reactions [124-127]. These results argue against a systemic, but in favor of a localized auto- and paracrine effect of adipose tissue on the intestine. While an unequivocal causal link between adipocytes, insulin sensitivity and intestinal inflammation is missing thus far, these observations provide a rationale for a mutual interplay between VAT and the intestine with its different compartments. Especially in the light of recently emerging exciting data linking visceral obesity and intestinal barrier function [121-123], a much deeper analysis of innate immune signaling in visceral adipocytes in conditions of intestinal health and disease is needed to further characterize the important role of VAT in intestinal homeostasis, and more generally their key role in the homeostasis of the whole organism.

VAT as part of the innate immune system in IBD

Besides its established role as an endocrine organ [128,129], the adipose tissue can be regarded as part of the innate immune system [2,3,44,130], being activated by inflammatory or infectious processes. Moreover, the adipose tissue expresses the whole machinery of inflammation and innate immune activation, including classical cytokines (IL-1, IL-6, TNFα), chemokines [monocyte chemoattractant protein-1 (MCP-1); C-C motif chemokine ligand 2], complement components (C1q, C3a), TLRs, nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and C1q/TNF-related proteins [130]. Thus, VAT could link innate immune reactions during gut inflammation to adjacent adipose tissue alterations such as creeping fat [131-134].

TLRs are among the most prominent sensing molecules (pattern recognition receptors) recognizing molecular patterns (pathogen-associated molecular patterns, PAMPs) derived from bacteria and viruses [135,136]. The groups led by Shapiro and Scherer [137] were the first to describe a prominent role of the TLR4 and TLR2 system in adipocytes. Following these reports, adipocytes have been shown [1,137-142] to express all known TLRs from TLR1 to TLR9, apart from TLR5 (flagellin receptor), and functionality has been demonstrated for all of them [1,143]. Table 5 summarizes the currently available data on the expression of TLRs and their functional activation by specific ligands in adipocytes. These data are complicated by the fact that adapter molecule utilization may differ in adipocytes when compared to classical immune cells. For example, Poly(I:C) signaling via TLR3 requires a Toll/IL-1 receptor-domain-containing adapter-inducing interferon(TRIF)-independent but myeloid differentiation primary response gene 88 (MyD88)-dependent route [144]. In contrast, LPS signaling via TLR4 requires MyD88, myelin and lymphocyte protein (Mal) and TRIF, whereas Pam3Cys signaling via TLR2 requires MyD88 and Mal, but not TRIF [144]. It has been proposed that the TLR system in adipocytes orchestrates the complex process of energy utilization in the context of immune responses

Table 5 Summary of data on Toll-like receptor (TLR) expression and activation by specific ligands in adipocytes

Expression	Activation	Effect	Reference
TLR1/2	Pam(3)Cys MALP-2	Release of IL-6, IL-8, MCP-1, TNFα Release of MCP-1	[1,139,143,144] [143]
TLR2/6	MALP-2	Release of IL-6, IL-8, MCP-1	[1,144]
TLR3	Poly (I:C)	Release of IL-6, IL8, MCP-1, IP-10 Inhibition of resistin secretion	[1,144,170] [1]
TLR4	LPS Unsaturated fatty acids Unsaturated fatty acids	Release of IL-6, IL-8, MCP-1, TNFα Inhibition of resistin secretion Release of MCP-1, resistin	[1,137,139,141,143,144] [1] [138]
TLR5	Flagellin	No effect	[1]
TLR7/8	Poly (U)	Inhibition of resistin secretion	[1]
TLR9	CpG	Inhibition of resistin secretion	[1]

TLR, Toll-like receptor; Pam(3)Cys, Pam3Cys-Ser-(Lys) 4, a synthetic triacylated lipopeptide (LP) that mimics the acylated amino terminus of bacterial LPs; MALP-2, macrophage activating lipopeptide-2; Poly (I:C), polyinosinic, polycytidylic acid, structurally similar to double-stranded RNA; LPS, lipopolysaccharide; Poly (U), poly-uridylic acid, structurally similar to single-stranded RNA; CpG, CpG-Oligodeoxynucleotide; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; CCL2, C-C motif chemokine ligand 2; TNFα, tumor necrosis factor α; IP-10, interferon gamma-induced protein 10; CXCL10, C-X-C motif chemokine 10

and immune activation [144,145]. However, since increased intestinal permeability leads to a direct exposure of adjacent VAT to microbial products, these data at the same time provide the molecular basis for IBD-associated inflammation of VAT.

In contrast to TLRs, the NOD-1 and NOD-2 proteins represent cytoplasmic receptors (NLRs) of the innate immune response. Since NOD-1 and NOD-2 are expressed in adipose tissue [146,147], these molecules not only might be involved in the pathogenesis of type 2 diabetes mellitus and obesity-related inflammation [136,147], but also might be activated in response to intestinal inflammation and microbial translocation. Activation of NOD proteins by NOD-1-specific ligands in adipocytes causes NF-κB p65 nuclear translocation and subsequent MCP-1, IL-6 and IL-8 production [147]. These results provide the molecular basis for the hypothesis that direct exposure of intestinal adipocytes to bacterial peptidoglycans could start the process of adipose tissue inflammation during gut inflammation. NLR protein-3 (NLRP3) represents an innate immune sensor, and its activation by microbial or endogenous danger signals causes caspase-1 activation and production of proinflammatory cytokines such as IL-1 and IL-18 [148]. NLRP3 activation by endoplasmic reticulum stress in adipocytes increases IL-1 expression and secretion [149], whereas repressors of NLRP3 reduce adipose tissue inflammation [150]. In mice deficient in NLRP3 expression, the defective inflammasome compartment was accompanied by reduced MCP-1 expression in adipocytes [148]. However, in spite of the well-known proinflammatory effects of a high-fat diet, such as adipose tissue macrophage infiltration, NLRP3 expression was not modified by a high-fat diet [142].

In summary, intestinal adipocytes residing within the VAT adjacent to inflamed gut express major functional components of the innate immune recognition system, such as TLRs and NODs/NLRPs. Consequently, visceral adipocytes are able to sense a wide variety of microbial components that cross the disturbed intestinal barrier seen in IBD [131]. Thus, the observed inflammatory transformation of VAT seems to be a consequence, rather than the cause of IBD. The physiological meaning behind this mechanism is most likely to provide an additional antimicrobial barrier surrounding the affected gut. This adipose tissue barrier might reduce the risk of intestinal perforation, bacterial translocation to the peritoneum and finally, systemic inflammation and sepsis [112]. Remarkably, a recent study published in *Science* in 2015 demonstrated that adipocytes protect against invasive bacterial infection by secreting antimicrobial peptides such as cathelicidin [117,151]. Thus, whereas VAT mass is clearly associated with obesity-related inflammation, insulin resistance and type 2 diabetes mellitus [152], intra-abdominal fat could be of benefit in IBD [103,112]. Whether viable bacteria are able to reside within adipocytes, and if so for how long, remains an additional important and unsolved question [103,153].

Fig. 1 depicts this hypothesis regarding the role of inflamed VAT in IBD. Because of the increased permeability of the mucus and epithelium, microbes and toxins are able to cross the mucus and epithelial barriers, which represent the first and second barrier. Subsequently, PAMPs are recognized by TLRs and NLRs in lamina propria mononuclear cells and in adipose tissue. Activation of TLRs and NLRs causes adipose tissue inflammation, hypertrophy and finally the formation of creeping fat. This altered adipose tissue releases cytokines, adipokines, chemokines, complement factors, antimicrobial peptides, and CTRPs, thus providing an additional barrier of local defense.

Concluding remarks

Current data suggest an intricate relationship between intestinal inflammation and adjacent VAT depots. During intestinal inflammatory conditions, VAT is not merely a passive "bystander", but actively participates in immune responses via the secretion of fat-derived hormones, the so-

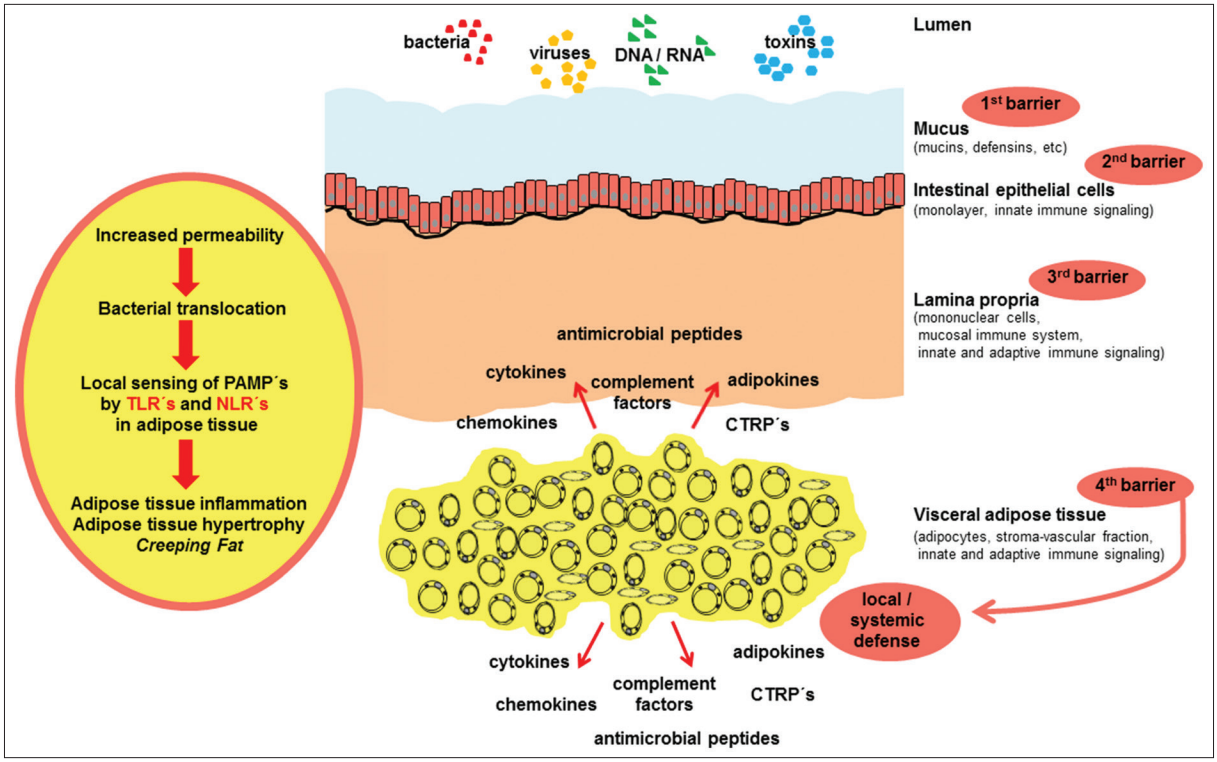

Figure 1 Current hypothetical view of the role of visceral adipose tissue in inflammatory bowel disease
The intestinal mucus provides a first barrier against luminal toxins and invading pathogens. In the context of intestinal inflammation and increased permeability of the mucus and epithelium, microbes and toxins are able to cross the epithelial and mucus barriers. Subsequently, lamina propria mononuclear cells interact with these compounds. When invasion cannot be contained by the mucosal compartment, pathogen associated molecular patterns (PAMPs) are recognized by Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs) in adipose tissue. Activation of TLRs and NLRs causes adipose tissue inflammation, hypertrophy and the formation of creeping fat. This altered adipose tissue releases cytokines, adipokines, chemokines, complement factors, antimicrobial peptides and C1q/tumor necrosis factor-related proteins (CTRPs), thus providing a "fourth barrier" of local defense. This mechanism might protect against local gut perforation, local peritonitis, systemic inflammation, and sepsis

called adipokines. Furthermore, adipocytes, via the expression of pattern recognition receptors, actively participate in anti-microbial host defenses in the context of intestinal bacterial translocation, as part of the innate immune system. Thus, VAT constitutes a barrier against invading pathogens and contributes to the homeostasis of the whole organism (Fig. 1). This mechanism could protect the organism from local gut perforation, local peritonitis, systemic inflammation and sepsis. Today, many questions in this innovative field remain unanswered. However, with the rapidly growing body of evidence, modulators of adipose tissue function and regulators of adipokine secretion, as well as modifiers of adipocytic pattern recognition molecules, might turn out to be future drug targets in the treatment of IBD.

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