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Review

Leptin, adiponectin, resistin, and ghrelin – Implications for inflammatory bowel disease

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Inflammatory bowel disease (IBD) is characterized by anorexia, malnutrition, altered body composition, and development of mesenteric white adipose tissue (WAT) hypertrophy. Increasing evidence suggests that adipokines synthesized either in WAT or in immune cells, are involved in these manifestations of IBD. Among adipokines leptin, adiponectin and resistin hold a fundamental role while the role of ghrelin in inflammation is not well established. Preliminary studies have shown overexpression of leptin, adiponectin, and resistin in mesenteric WAT of patients with Crohn's disease (CD) and significant alterations of circulating serum levels of these adipokines in IBD. It has also been demonstrated that intestinal inflammation causes an increase in endogenous ghrelin production. In animal models of intestinal inflammation, existing data suggest that leptin, adiponectin, and resistin are pivotal mediators of inflammation. Interesting therapeutic interventions based on these data have been suggested. A specific role for hypertrophic WAT has also been implicated in CD. Further efforts with experimental and clinical studies are needed to better understand the role of adipokines in IBD.

Keywords: Adiponectin / Ghrelin / Inflammatory bowel disease / Leptin / Resistin

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1 Introduction

White adipose tissue (WAT) has emerged as an important endocrine and signaling tissue during the last two decades. Accumulating evidence suggests that a variety of WAT cells (adipocytes, matrix cells, stromovascular cells, macrophages, and mast cells) produce and release a great number of bioactive proteins, including multifunctional molecules that are secreted by many tissues, and proteins that are exclusively produced by WAT [1]. They are collectively called "adipokines" (Table 1).

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Abbreviations: CD, Crohn's disease; **CRP,** C-reactive protein; **DC,** dendritic cells; **GH,** growth hormone; **GHS-R,** growth hormone secretagogue receptor; **HC,** healthy controls; **hHSC,** human hepatic stelate cells; **IBDs,** inflammatory bowel diseases; **KO,** knock-out; **MCP-1,** monocyte chemo-attractant protein-1; **mWAT,** mesenteric white adipose tissue; **NF-kB,** nuclear factor-kappaB; **NK cells,** natural killer cells; **PBMC,** peripheral blood mononuclear cells; **PMNC,** polymorphonuclear cells; **PPARγ**, peroxisome proliferators-activated receptor-γ; **RA,** rheumatoid arthritis; **SNPs,** single nucleotide polymorphisms; **TNFα**, tumor necrosis factor α; **UC,** ulcerative colitis; **WT,** wild type

An intense research is taking place on the interaction between WAT, inflammation, and immunity, based on the fact that many adipokines are inflammation-related proteins. Following the observation that obesity is a state of low-grade inflammation, a number of studies focused on the role of adipokines in various chronic inflammatory diseases [2]. Anorexia, malnutrition, altered body composition, and development of mesenteric WAT (mWAT) hypertrophy (accumulation of intra-abdominal mWAT), are well-known features of inflammatory bowel diseases (IBDs) mainly of Crohn's disease (CD). An aberrance in adipokines' secretion seems to be critically involved into the pathogenesis of IBD [3, 4].

Ghrelin is the endogenous ligand for the growth hormone secretagogue receptor 1a (GHS-R1a). Although GHSR1a is mainly expressed at central neuroendocrine tissues, a widespread pattern of expression has also been demonstrated in a variety of peripheral tissues including stomach and neuronal cells of the gut [5]. Major focus of research with ghrelin has been primarily related to the regulation of food intake and its accompanying endocrine functions. However, given the wide distribution of functional GHS-R on various immune subsets, it was hypothesized that this peptide may exert immunoregulatory effects on immune cell subpopulations [6].

Table 1. Classification of WAT products according to their mode of action

Classical cytokines	TNFα, IL-1β, IL-1RA, IL-6, IL-10, IL-15, IL-17D, IL-18
Chemokines	IFNγ, IP-10 (or CXCL 10), IL-8 (or CXCL 8), MCP-1 (or CCL 2), MIF, RANTES (or CCL 5)
Growth factors	TGFαβ, NGF (neurotrophin), HGF, MCSF, insulin growth factor (IGF)-1, GM-CSF, LIF, VEGF
Members of the CTRP-family	Cartonectin (CORS-26)
Members of C1q/TNFα superfamily	C1q, adiponectin, C1QDC1, C1QTNF3
Adipocyte-specific transcription factors	PPARγ, ADD1/SREBP1c, KLF-5, RXRα, KROX-20, C/EBPα,β,δ
Proteins participating in the alternative complement pathway	Adipsin, factor B, C3a, ASP, CR1, properdin
Proteins for vascular haemostasis	PAI-1, tissue factor
Proteins involved in the regulation of blood pressure	Renin, AGT, angiotensin I and II, ATI and II, ACE, chymase, cathepsins D/G/S, tonin
Proteins involved in lipid metabolism	FABP, RBP4, CETP, apolipoprotein E, zinc-α2-glycoprotein
Proteins involved in steroid metabolism	Cytochrome P450-dependent aromatase, LDL, 17βHSD, 11βHSD1
Acute-phase and stress proteins	Haptoglobin, metallothionein, SAA 1 & 2, CRP
Proteins with various functions	Leptin, resistin, hepcidin
New adipokines	Omentin, apelin, visfatin, vaspin, chemerin

IP-10, inducible protein-10; MIF, macrophage migration inhibitory factor; RANTES, regulated upon activation normal T-cell express sequence; TGFαβ, transforming growth factor alpha and beta; NGF, nerve growth factor; HGF, hepatocyte growth factor; MCSF, macrophage colony-stimulated factor; GM-CSF, granulocyte-macrophage CSF; LIF, leukemia inhibitory factor; VEGF, vascular endothelial growth factor; CORS-26, collagenous repeat-containing sequence of 26 kDa protein; C1QDC1, C1q domain containing 1; C1QTNF3, C1q & TNF related protein 3; ADD1/SREBP1c, adipocytes determination & differentiation-dependent factor 1/sterol regulatory element binding protein-1; KLF-5, Krüppel-like transcription factor; RXRα, retinoid X receptor α; KROX-20, Krox-20 homolog Drosophila; C/EBPα,β,δ, CCAAT enhancer-binding proteins α,β,δ; ASP, acylation-stimulating protein; PAI-1, plasminogen activator inhibitor-1; AGT, angiotensinogen; ATI and II, angiotensin receptors type I and II; ACE, angiotensin-converting enzyme; FABP, fatty acid-binding protein; RBP4, retinol-binding protein 4; CETP, cholesteryl ester transfer protein; LPL, lipoprotein lipase; SAA 1 and 2, serum amyloid-A proteins 1 and 2.

Among adipokines leptin, adiponectin and resistin hold a fundamental role while the role of ghrelin in inflammation is not well documented. Here, we present an updated overview of the key developments on the relation of these proteins with inflammation and immunity, especially focusing on their proposed participation in intestinal inflammation. A speculation about the possible role and importance of mWAT and adipokines in the pathogenesis of IBD is also provided.

2 Leptin

Leptin is a 16 kDa nonglycosylated protein, member of the type I cytokine superfamily with a long chain four-helical bundle structure [7]. It is mainly produced by adipocytes in direct proportion to WAT mass and this secretion is greater from subcutaneous (sc) compared to visceral WAT [8]. Plasma leptin in humans ranges within a few ng/mL and circulates partially bound to plasma proteins. Protein-bound leptin exists in equilibrium with free leptin and the latter represents the bioactive hormone [9]. Leptin release and mRNA expression positively correlated with the size of the adipocytes [10].

Besides its metabolic and endocrine functions, leptin is also a modulator of various immune and inflammatory responses (Table 2). Humans with congenital leptin deficiency have a much higher incidence of infection-related death during childhood [11]. Leptin's functional receptor (ObRb) is expressed in all cell types of innate and adaptive immunity. Leptin induces activation, modifies cytokine production pattern towards a Th1 response (promoting the release of IL-2 and IFNγ and inhibiting IL-4 secretion) [12], and directly stimulates the expression and release of IL-1α, IL-1β, IL-6, and TNFα by T-cells [13].

Leptin modulates the hyporesponsiveness and proliferation of $Foxp3^+CD4^+CD25^+$ regulatory T (Treg) cells both *in vitro* and *in vivo*. Human Treg-cells have been found to produce substantial amounts of leptin which was responsible for an autocrine inhibitory loop that constrained their expansion. In line, leptin's neutralization inhibited the proliferation of effector $CD4^+CD25^-$ T-cells and led to an expansion of Treg-cells. It seems that these opposing effects of leptin blockage on effector and regulatory T-cells are associated with a differential expression of intracellular leptin and cell-surface ObRb in the two cell subsets [14]. Similarly, leptin promoted differentiation of peripheral blood-derived dendritic cells (DC), protected them from apoptosis, modulated cytokine production, and licensed them for Th1 priming of $CD4^+$ T-cells [15]. An attempt of generating DC from the bone marrow of *db*/*db* (leptin receptor-deficient) mice, ended in a lower yield of cells compared to their wild type (WT) counterparts and also to an expression of lower levels of costimulatory molecules, higher rates of apoptosis, lower production of IL-12 and TNFα, and lower stimulatory capacity towards allogenic $CD4^+$ T-cells [16].

Table 2. Main effects of leptin related to inflammation and IBD

Target organ/tissue	Normal effect
Adipose tissue	Stimulation of lipolysis – prevention of ectopic lipid deposition
Vessels	Involvement in angiogenesis
Bone marrow	Regulation of hemopoiesis
Cell type	**Inflammatory effect**
T-cells	Pro-: ↑ IL-1α, IL-1β, IL-6, TNFα, IL-2 & IFNγ ↓ IL-4 ↓ $CD4^+CD25^+$ proliferation, ↑ $CD4^+CD25^-$ proliferation
PBMC, macrophages	Pro-: GH, TNFα, IL-6, IL-12, CCL2, IFNα, eicosanoid & NO ↑ Anti-: IL-1Ra ↑
DC	↑ Differentiation, cytokine production, ↓ apoptosis
PMNC	↑ Neutrophil activation (CD11b), chemotaxis, ROS
NK cells	↑ Proliferation, differentiation, activation, cytotoxicity
Colonic epithelial cells (UC)	↑ Leptin expression & release ↑ leptin-induced neutrophil infiltration
Inflamed mesenteric adipocytes (IBD)	↑ Leptin expression
Hepatocytes	↑ Leptin-mediated CRP production
Serum (IBD)	Diverse: ↑ or ↓ or unaltered

In peripheral blood mononuclear cells (PBMC) leptin stimulates the production of TNFα, IL-6, IL-12, IFNα, and induces eicosanoid and nitric oxide synthesis [17, 18]. These cells are activated by leptin *via* expression of surface markers [19]. In polymorphonuclear cells (PMNC) of healthy subjects, leptin leads to an increase in CD11b expression and also stimulates reactive oxygen species production and chemotaxis [20]. In natural killer (NK) cells it influences their proliferation, differentiation, activation, and cytotoxicity [21]. However, leptin shows also potent anti-inflammatory properties, since it stimulates the expression and production of IL-1Ra [22]. These effects of leptin indicate a different pattern of influence to each component of immunity: leptin deficiency seems to result in attenuated adaptive immune-mediated response, whereas influence innate immune response towards an inadequate control of inflammation.

The role of leptin in inflammation seems to be associated with prolonged anorexia despite weight loss, a common finding in patients with IBD, and failure of the normal compensatory responses that must operate after a poor feeding period [23]. In animal models of intestinal inflammation, leptin behaves as a pivotal mediator of inflammation [24]. $CD4^+CD45RB^{high}$ T-cells from *db*/*db* mice do not induce colitis as rapidly as do $CD4^+CD45RB^{high}$ T-cells from non-*db*/*db* mice, when transferred to T-cell-deficient (*scid*) mice [25]. Subcutaneous transplantation of WAT from WT littermates increased leptin and normalized metabolic, immune and inflammatory parameters of *ob*/*ob* (leptin-deficient) mice [26]. Also, chemically induced intestinal inflammation in rats resulted in elevated circulating leptin levels which correlate with the degree of inflammation and the development of anorexia [27].

In contrast, administration of leptin ameliorated acetic acid-induced colitis in rats [28]. Also, a chronic but not an acute stimulation with proinflammatory cytokines caused a suppression of leptin in culture-differentiated human adipocytes [29]. ObRb is present in brush border, basolateral membrane, and cytoplasm of enterocytes [30]. Inflamed colonic epithelial cells from ulcerative colitis (UC) patients expressed and released leptin into the intestinal lumen. Leptin in turn, induced epithelial wall damage and neutrophil infiltration [31].

An overexpression of leptin mRNA in mWAT was reported in IBD patients compared to controls, indicating that leptin might participate in the inflammatory process by enhancing mesenteric TNFα expression [32]. Our group showed that serum leptin levels were decreased in IBD patients compared to healthy controls (HC), irrespective of sex, age, C-reactive protein (CRP), years of diagnosis, and disease activity and localization. Patients with BMI < 25 had lower serum leptin levels compared to patients with BMI ≥ 25 [33]. In previous studies, results on serum leptin levels were diverse [34 – 37]. Treatment of CD patients with infliximab (an anti-TNFα agent) significantly increased leptinaemia, implying that TNFα exerts a major inhibitory action on leptin production in these patients [38].

3 Adiponectin

Adiponectin is an approximately 30 kDa polypeptide with 247 amino acids that contains an N-terminal signal sequence, a hypervariable domain with no interspecific homology, a collagen-like domain, and a C-terminal globular domain [39]. The terminal structure of the globular domain bears a striking similarity to TNFα, despite a lack of homology in primary sequence [40]. A proteolytic cleavage product containing the globular domain of adiponectin also circulates at significant levels and has biological activity. Adiponectin is mainly expressed by mature adipocytes and circulates at high levels in the bloodstream (5 – 10 mg/mL,

Table 3. Main actions of adiponectin related to immune system and to IBD

Cell type	Inflammatory effect
3T3-L1 cells	Anti-: ↓ adiponectin production under oxidative stress
Human cultured adipocytes	Anti-: ↓ TNFα, adiponectin production in presence of IL-6 Pro-: ↑ TNFα-mediated acute adiponectin production ↑ IL-1β, IL-6, TNFα PGF_{2a}, PGE
THP-1 cells	Anti-: ↑ apoptosis, ↓ scavenger receptor A (LMW & HMW) ↑ LPS-mediated IL-6, ↑ IL-10 (LMW) Pro-: ↑ IL-6 (HMW)
HT-29 cells	Pro-: ↑ proliferation (FL & G), IL-8, GM-CSF, MCP-1 (G)
Intestinal epithelial cells in KO mice	Anti-: ↑ colitis severity adiponectin attenuated colitis Pro-: ↓ colitis severity, adiponectin restored inflammation, binded with HB-EGF, bFGF
T-cells	Anti-: ↓ responses
PBMC, macrophages	Pro-: ↑ LPS-induced IL-8, phagocytosis (HMW), TNFα, IL-6 (G) Anti-: ↓ TNFα, IL-6, IFNγ, NF-κβ, phagocytosis ↑ IL-10, IL-1Ra
DC	↑ IL-10, IL-1Ra
NK cells	↓ IFNγ, IL-2 mediated cytotoxicity
Stem cells	Anti-: ↓ proliferation of macrophage progenitors Pro-: ↑ proliferation of primitive hemopoietic stem cells
Inflamed mesenteric adipocytes (IBD)	↑ Adiponectin expression ↑ cell proliferation and differentiation of pre-adipocytes to adipocytes
Serum (IBD)	↑

LMW, low molecular weight; HMW, high molecular weight; FL, full-length adiponectin; G, globular adiponectin.

0.01% of total serum protein). After production, it forms trimers (low molecular weight (LMW) complexes) which further polymerize into hexamers (middle MW complexes) and 12- to 18-mers (high MW (HMW) polymeric complexes 180–600 kDa) [41]. Adiponectin's release was also found to be positively related to adipocyte size [10] and its expression is higher in sc than visceral WAT [8].

The role of adiponectin in inflammation seems conflicting, although it is generally considered as an anti-inflammatory agent (Table 3). Adiponectin and TNFα suppress each other's production and antagonize each other's action in their target tissues [42, 43] and IL-6 decreased adiponectin levels *in vitro* [43]. Adiponectin induced the production of IL-10 and IL-1Ra in human PBMC, macrophages and DC and impaired the production of IFNγ in macrophages. Adiponectin-treated macrophages exhibited a reduced phagocytic capacity and allogenic T-cell response [44]. A protective effect of adiponectin against oxidative stress has also been implicated [45] while oxidative stress caused a decrease in adiponectin secretion in 3T3–L1 adipocytes [46]. Adiponectin has been found to suppress IL-2-enhanced cytotoxic activity of NK cells and production of IFNγ [47]. It also inhibited the proliferation of macrophage progenitors [48] but favored proliferation of a population consisting of the most primitive hemopoietic stem cells [49]. Recently, the globular head of adiponectin was shown to bind various chemokines like stromal cell-derived factor-1 (SDF-1), CCF 18, RANTES, monocyte chemo-attractant protein-1 (MCP-1), and macrophage inflammatory protein-1alpha (MIP-1α) and both adiponectin and SDF-1 were clearly detected at vascular walls in the gut of bone marrow-transplanted patients with severe diarrhea due to acute intestinal graft-*versus*-host disease [50].

On the other hand, acute stimulation of culture-differentiated adipocytes with TNFα increased adiponectin's production. Gradually this effect was blunted and over 24 h treatment total adiponectin release was unchanged [29]. Globular adiponectin induced TNFα and IL-6 secretion in human peripheral macrophages [51] and also stimulated the release of IL-1β, IL-6, TNFα, prostaglandin F_{2a} (PGF_{2a}), and PGE from human WAT [52]. In the presence of LPS, HMW adiponectin augmented the translation of IL-8 and phagocytosis of late apoptotic cells by human macrophages [53].

The highest biological activity appears to be exerted by trimers, however certain functions like nuclear factor kappaB (NF-κB) activation can be caused only by higher complexes. Both LMW and HMW forms induced apoptosis in nondifferentiated monocytic THP-1 cells and reduced macrophage scavenger receptor A mRNA expression. However, HMW form induced IL-6 secretion in human monocytes while LMW form reduced LPS-mediated IL-6 release and furthermore stimulated IL-10 secretion and the key molecule for this difference seems to be NF-B [54].

Both globular and full length adiponectin stimulated proliferation and exerted synergistic action in combination with IL-1β in HT-29 cells but only globular adiponectin proved a potent stimulant of IL-8, granulocyte-macrophage colony stimulating factor (GM-CSF) and MCP-1 secretion. This observation could be important in colonocytes' role concerning defense against enteric pathogens and perpetuation of inflammation in IBD [55]. In two experimental studies, where adiponectin knock-out (KO) mice were used, adiponectin's effect on murine colitis was totally diverse. In the first study, adiponectin KO mice developed much more severe colitis compared to WT littermates and adenovirus-mediated supplementation of adiponectin significantly atte-

nuated the severity of colitis. Moreover, adiponectin inhibited LPS-induced IL-8 production in HT-29 cells *in vitro*, suggesting that it has a direct anti-inflammatory effect on intestinal epithelial cells [56]. In the second study, adiponectin KO mice were protected from chemically induced colitis, while administration of adiponectin restored inflammation. Adiponectin increased production of IL-6 and MIP-2 in colon cultures. In serum, it bound to heparin binding epidermal growth factor (HB-EGF) and basic fibroblast growth factor (bFGF) [57]. Finally, both adiponectin and its major receptors (adipoR1 and adipoR2) are expressed in the colon and luminal adiponectin is associated with colonic epithelial cells [56 – 58].

The role of adiponectin in IBD has recently attracted scientific interest. Adiponectin's production is enhanced in hypertrophied mWAT in contact with the involved intestine of CD patients and this overexpression is higher than in UC patients and patients operated on for colon cancer (control group) [59]. Paul *et al.* also showed a higher secretion of adiponectin from mWAT in operated CD patients compared to diverticulitis and colon carcinoma patients. Steroid treatment was found to reduce adiponectin's secretion rate [60]. Our group showed that mean serum adiponectin levels are increased in IBD patients compared to HC [33] and that anti-TNFα treatment had no significant impact on these levels, although there was a trend for a decrease (unpublished data). Similarly, in patients with alcoholic hepatitis, treatment with infliximab resulted in a long-lasting decrease of circulating adiponectin and in hepatitis B and C virus-infected patients circulating adiponectin levels decreased after IFNα therapy [61, 62].

In a population-based study increased levels of serum adiponectin in women were associated with a decrease in bone mineral density, even at nonload bearing sites and after adjustment of measures of body fat, suggesting that adiponectin may play a role in bone metabolism *via* menopausal status. This finding in correlation with our finding of increased serum adiponectin levels in IBD patients could engage adiponectin in the IBD-associated osteoporosis especially in postmenopausal women [63].

4 Resistin

Resistin is a 12.5 kDa cysteine-rich peptide consisting of 108 amino acids. This molecule includes a signal peptide, a variable region, and a conserved C-terminus [64]. It belongs to a family of resistin-like molecules with distinct expression patterns and biological effects [65]. The mature protein has a tendency to form oligomers, thus circulating in human serum in several different LMW and HMW isoforms [66]. Its serum concentration in humans ranges from 7 to 22 ng/mL. The major cell populations that express and produce resistin in humans are PBMC, macrophages, and bone marrow cells [67, 68]. Data on resistin production from human adipocytes are diverse. Existing studies support this production [69 – 71] but recently, human preadipocytes and isolated fat cells were clearly devoid of resistin mRNA, providing the suggestion that human resistin should not be acknowledged as an adipose-secreted hormone but as a specific myeloid-derived cytokine [72]. Higher levels of resistin mRNA expression were observed in abdominal sc and omental depots in comparison with thigh and mammary fats [69].

The role of resistin in inflammation has been extensively studied in the last few years. (Table 4). In PBMC resistin mRNA expression and protein release are strongly increased following the effect of TNFα, IL-1, IL-6, and LPS *in vitro*, probably through NF-κB activation [73, 74]. Stimulation of human abdominal sc adipocytes with LPS increased resistin secretion an effect not seen with TNFα and IL-6 [75]. Experimental endotoxinemia in healthy volunteers induced a dramatic elevation of circulating resistin levels [74]. Resistin accumulated locally in the inflamed joints of patients with rheumatoid arthritis (RA) and its levels correlated with the intensity of inflammation as defined by the intra-articular white blood cell count and IL-6 levels but the effect concerning systemic markers of inflammation such as erythrocyte sedimentation rate and CRP is diverse [76, 77]. Resistin was found in plasma cells, macrophages, B lymphocytes and some synovial fibroblasts in synovial tissue samples of patients with RA and osteoarthritis. Serum but not synovial resistin levels were positively associated with CRP in RA patients [78].

Stimulation of PBMC with resistin markedly induced the genes and cytokine release for TNFα, IL-1β, and IL-6 and resistin mRNA itself (positive feedback mechanism) [77]. Addition of recombinant human resistin resulted in enhanced secretion of TNFα and IL-12 from macrophages independently of resistin forms [79] and of TNFα, IL-6, and toll-like receptor 2 (TLR-2) from adipocytes [75]. Rosiglitazone reduced resistin-stimulated increased secretion of TNFα and IL-6 from adipocytes [75]. Exposure of human hepatic stelate cells (hHSC) to recombinant resistin for 24 – 48 h induced an increase in MCP-1 and IL-8 in the culture medium but resistin did not increase hHSC proliferation [80]. Resistin upregulated the expression of vascular cell-adhesion molecule 1 (VCAM1), intercellular adhesion molecule 1 (ICAM1), and CCL2 by human endothelial cells and induced these cells to release endothelin-1 [81]. Finally, plasma resistin concentration in a population-based cohort was positively associated with leukocytes and highly sensitive CRP [82].

The study of resistin in IBD includes serum and tissue measurements. Resistin secretion from the mWAT of patients operated on for colon cancer or diverticulitis was found significantly lower compared with the secretion from the creeping fat contiguous to the involved intestine in patients with CD, where treatment with steroids reduced resistin production [60]. Our group demonstrated that mean

Table 4. Resistin's interaction with the immune system, inflammation, and IBD

Cell type	Inflammatory effect
Human cultured adipocytes	↑ LPS-mediated resistin production ↑ resistin-induced TNFα, IL-6, TLR-2
PBMC, macrophages	↑ TNFα, IL-1, IL-6 and LPS-induced resistin release ↑ resistin-induced TNFα, IL-1β, IL-6, IL-12, resistin
Plasma cells, B cells (activated)	↑
Synovial fibroblasts (inflamed)	↑
hHSC	↑ Resistin-induced MCP-1, IL-8
hEC	↑ Resistin-induced VCAM-1, ICAM-1, CCL2, ET-1
Inflamed mesenteric adipocytes (IBD)	↑ Resistin expression
Serum (IBD)	↑

hHSC, human hepatic stelate cells; hEC, human endothelial cells; ET-1, endothelin-1.

serum resistin in IBD patients is increased compared with HC and this increase is similar for patients with active and quiescent disease [33]. Moreover, we observed that anti-TNFα treatment caused a significant decrease in serum resistin levels in IBD patients (unpublished data).

5 Ghrelin

Ghrelin was first reported in 1999, as a 28 amino-acid peptide with a fatty acid chain modification on the N-terminal third residue (octanoylation of serine-3 position) [83]. Acylation seems essential for binding of ghrelin to the GHS-R1a and for most of its actions. Nonacylated ghrelin (or des-octanoyl or des-acyl) circulates in far greater amounts than the acylated (or *n*-octanoyl) form. It does not displace ghrelin from its hypothalamic and pituitary binding sites and is unable to stimulate growth hormone (GH) release *in vivo*. However, studies report several biological effects of des-octanoyl ghrelin [84].

Ghrelin was originally isolated from the stomach. A smaller number of immunopositive cells are found in the small (mainly in the duodenum and jejunum) and large intestine [84]. In the lower gastrointestinal (GI) tract ghrelin cells exist in both types of GI endocrine cells: either in no contact with the lumen, the so-called "closed" cells, similar to the stomach or elongated "open" cells communicating with the lumen [85]. Interestingly, GHS-R immunoreactivity has been demonstrated within the enteric nervous system of both stomach and intestine and an absence of GHS-R is found from smooth muscle cells and epithelia [86]. It has been suggested that the majority of circulating ghrelin originates from the stomach, with a smaller proportion (∼30%) from the small intestine. Ghrelin gene expression is decreased by administration of leptin and IL-1β [84].

Acylated ghrelin inhibited basal and TNFα-induced release of IL-8 and MCP-1, blocked NF-κB activation, prevented PBMC adhesion to endothelial cells in cultured human umbilical vein endothelial cells (HUVECs) and abolished cytokine release induced by systemic administration of endotoxin *in vivo*, through interaction with GHS-R1a [87]. Ghrelin and GHS-R1a have been identified in T and B lymphocytes, PBMC and PMNC. T-cells have been shown to actively secrete ghrelin [13, 88]. Ghrelin inhibited IL-1β, IL-6, and TNFα production from activated human PBMC and T-cells and leptin-mediated proinflammatory cytokine protein and gene expression in these cells [13]. The latter observation implies that ghrelin and leptin, similar to their mutually antagonistic effects on food intake in hypothalamus, also exert reciprocal regulatory effects on inflammatory cytokine expression in the immune system. Moreover, ghrelin has been shown to increase prostacyclin production from endothelial cells [89]. Thus, ghrelin-induced inhibition of proinflammatory cytokine expression and production along with an increased prostacyclin production suggest that this hormone may serve as a potential therapeutic agent in ameliorating a wide variety of inflammatory conditions. Interestingly, human T-cells upon activation can produce 300–800 pg/mL of total ghrelin in the culture supernatants but also a raised production can be seen from B-cells and PBMC [13] (Table 5).

Absence of endogenous ghrelin decreased the disease activity index and delayed neutrophil infiltration in chronic dextran sulfate sodium (DSS)-induced colitis in ghrelin KO mice compared with WT [90]. Ghrelin and its receptor mRNA expression were upregulated in 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis in mice and ghrelin stimulated IL-8 promoter activity and production and activation of the NF-κB/IκB pathway in a human colonic epithelial cell line [91]. Conversely, administration of ghrelin in a similar animal model, either at the beginning of the disease or a few days after the establishment of colitis, ameliorated the clinical and histopathologic severity of the disease and this therapeutic effect was associated with down-regulation of both inflammatory and Th1-driven autoimmune response and increased levels of IL-10 [92]. We showed that serum ghrelin levels are elevated in IBD patients irrespective of the disease being active or quiescent and these levels were higher in male than female patients, higher in ileal compared to colonic CD and were correlated with lower leptin levels in IBD patients compared to HC [33]. On the other hand, Peracchi *et al.* [93] showed that cir-

Table 5. Actions of ghrelin related to IBD

Stomach, gut	Inhibition of leptin expression
WAT	Stimulation of adipogenesis: reduction in fat oxidation, increased food intake, stimulation of differentiation of preadipocytes
Cell type	**Inflammatory effect**
HUVECs	↓ IL-8, MCP-1 (basal & TNFα-mediated), NF-κB blockage ↓ endotoxin-induced cytokine release PBMC adhesion prevention
PBMC, macrophages	↓ TNFα, IL-1β, IL-6 and leptin-mediated cytokine release
T-cells	↓ TNFα, IL-1β, IL-6 and leptin-mediated cytokine release
hEC	↑ Prostacyclin production
Intestinal epithelial cells in KO mice	Pro-: ↓ colitis severity
Intestinal epithelial cells in non-KO mice	Pro-: ↑ colitis-induced ghrelin and GHS-R1a, IL-8, NF-κB/IκB Anti-: ↑ colitis severity Ghrelin-induced colitis amelioration, ↓ Th-1 response, ↑ IL-10
Serum (IBD)	Diverse: ↑ or ↓

HUVECs, human umbilical vein endothelial cells.

culating ghrelin was higher in patients with active IBD compared to HC and patients in remission.

6 Is there a role for mWAT and adipokines in differentiating CD from UC?

Alteration in body fat distribution, with a proliferation of intra-abdominal fat is a common finding in many patients with IBD, especially CD. Mesenteric WAT is mainly hypertrophied around the involved intestine in patients with CD, where axial polarity of inflammation is the mainstay. Fat-wrapping (or creeping fat) is defined as the progressive expansion of the mWAT from the mesenteric border to the antimesenteric surface of the small or large intestine which results to coverage of their circumference partially or totally and to the disappearance of the bowel-mesentery angle [94]. Histological examination of mWAT adjacent to involved intestine in CD patients reveals an increased infiltration mainly from macrophages and T-cells as well as a reduced size and an increased number of adipocytes [59]. Preadipocytes and macrophages seem to share particular genes expression patterns. A trans-differentiation of WAT stromovascular cells or 3T3-L1 preadipocytes to macrophages with acquirement of phagocytic properties has been shown [95].

A local activation of production of peroxisome proliferators-activated receptor-γ (PPARγ) from adipocytes due to stimulation from translocated bacteria entering through a defective epithelial barrier in CD has also been implicated as the cause of hypertrophy of mWAT [96]. In line, repeated TNBS-induced intestinal inflammation in rats caused a site-specific increase in mesenteric fat content, a decrease in the diameter of the adjacent to the bowel wall but not of perinodal mesenteric adipocytes, an increase in lipolysis and TNFα production in both sites but interestingly a reduction in PPARγ production and an elevation in leptin and adiponectin secretion only from perinodal adipocytes, indicating a site-specific interplay between these adipokines and the immune cells [97]. Also recently, 3T3-L1 preadipocytes were maintained in undifferentiated state, under continuous stimulation with LPS. They synthesized more proinflammatory products than differentiated adipocytes, like various chemokines but also leptin, adiponectin, resistin, and visfatin [98]. From these studies we can further support the dominance of the predifferentiated status of small adipocytes in inflamed mWAT and the importance this status has in the production of proinflammatory molecules.

The increased production of leptin in the inflamed mWAT either by adipocytes or by immune cells in CD patients could stimulate the release of various proinflammatory cytokines in an endocrine and also autocrine/paracrine way, driving the potential towards a Th1 response and influence PBMC activation and macrophage migration and aggregation into WAT. Leptin seems to affect the ratio of T-cell subpopulations towards an autoimmune and susceptible to infections status (suppression of regulatory and proliferation of effector T-cells) and also the function of DC. Leptin also stimulates hepatic CRP production, a predominantly elevated molecule in CD compared to UC patients [99]. Increased leptin production is even compatible with inflammation-mediated hypoxia affecting adipocytes, a situation frequently seen in the mWAT of involved intestine [100]. On the other hand, animal models of intestinal inflammation and studies on UC patients assume a central role for the epithelial cell and intraepithelial and lamina propria T-lymphocytes as the main producers of leptin in UC. In this case, leptin could result in the aggregation of neutrophils and maybe attenuation of apoptosis of the above-mentioned T-cells. The enhanced function of NK cells by leptin could also play a specific role in UC considering that increased numbers of activated NK cells have

been reported in UC [101]. Conversely, decreased serum leptin levels in both CD and UC patients could be partially attributed to chronic-state elevated circulating TNFα and reflect further IBD patients' susceptibility to infections due to impaired immune response. By blocking TNFα, serum leptin levels increase and this elevation also improves the function of the immune system.

Concerning adiponectin, the target cell and the type of inflammatory microenvironment may play a critical role in determining the action of adiponectin as a pro- *versus* anti-inflammatory molecule. Interestingly, adiponectin production and expression were decreased in human adipocytes cultured in a hypoxic environment [100]. These observations provide us with a possible two-face identity of adiponectin in CD. One hypothesis is that adiponectin is overproduced locally by abundant small-sized adipocytes in response to PPARγ overexpression in inflamed hypertrophied mWAT. In turn, adiponectin exerts its anti-inflammatory actions interfering with PPARγ in adipocytes and lamina propria macrophages. Abundant adiponectin causes an elevation in plasma levels developing a counter-regulatory mechanism towards systemic inflammation by affecting the function of PBMC through activation of PPARγ [102]. The divergent theory supports that adiponectin in a specific inflammatory environment, acts like a proinflammatory adipokine, further perpetuating chronic inflammation locally and systemically by promoting the release of proinflammatory cytokines and chemokines from either macrophages/PBMC or epithelial cells. In UC the possible role of adiponectin remains more obscure. Colonic epithelial cell probably holds again the key since it has been showed off as an important site of expression and production of adiponectin and its main receptors, indicating a possible autocrine loop of action. Whether adiponectin acts as an anti-inflammatory agent (competing IL-8 production? promoting angiogenesis? other mechanism?) or as a proinflammatory factor (enhancing IL-6 and MIP-2 production? binding with growth factors that are essential for maintaining colonic epithelial integrity? binding bacterial LPS thus modulating tolerance to bacterial antigens?) remains to be elucidated.

Although among IBD patients only CD are characterized by transmural inflammation and creeping fat, the existing few data do not permit us to conclude safely about differences in adipokines production between UC and CD.

7 Conclusions

Major research progress has been recently done towards the understanding of the role of leptin, adiponectin, resistin, and ghrelin in inflammation and immune-related processes. It is now clear that the first three are proteins synthesized by various cell types, circulate in variable concentrations, function in a hormone-like manner, and elicit classic cytokine properties. Increasing evidence suggest that these molecules are actively involved in acute inflammation [103], but also in many chronic diseases including intestinal inflammation and especially IBD.

Leptin's role seems fundamental in Th1-mediated autoimmune diseases, like CD. So blocking peripheral leptin action (*e.g.*, *via* anti-leptin or anti-ObRb antibodies) could perhaps improve the disease status. Of course, we cannot predict the effect of such treatment on the innate *versus* the adaptive arm of immunity.

Adiponectin's role includes the divergency between its various forms. Full-length can be cleaved to globular adiponectin, mainly by PMNC-produced elastase a cell subpopulation in abundance in intestinal inflammation. Measuring adiponectin's levels and mRNA expression in the intestine in IBD patients and HC could be a first step in elucidating its role. Further on, determining the complex-LMW or HMW-that predominates in the intestine and the subsequent ratio might provide further clues. Finally, the study of various single nucleotide polymorphisms (SNPs) of adiponectin gene could add data since reduced adiponectin levels associated with SNPs, have been linked to inflammatory diseases like the metabolic syndrome [104].

Resistin seems to be a significant factor in the inflammatory process associated with IBD, probably more important than adiponectin and leptin. Several topics involved in resistin's functional role remain obscure. First, the contributory effect of LMW and HMW isoforms in inflammation has not been clarified. Some biological actions of resistin seem to need oligomerization, like in cardiac muscle cells, in contrast with its role in the liver [105]. Second, certain SNPs seem to alter resistin's behavior in various inflammatory environments but also in serum [106 – 108]. Third, the identification of resistin mRNA expression and release, if any, from intestinal epithelial cells under inflammatory conditions would give valuable information concerning the possible different behavior of this adipokine in CD and UC. Concerning mWAT in CD patients, it has to be further clarified if a difference exists regarding the cell compartment (adipocytes or monocytes) that mainly contributes to resistin's production and this information could point the target site for its inhibition.

The role of ghrelin as a pro- or anti-inflammatory molecule in peptic inflammation is still diverse. According to its anatomic location in the gut ghrelin can act as an endocrine but also as an autocrine/paracrine molecule and this probably depends on the environment. The pattern becomes more complex when taking into account the ghrelin-mediated enteric nervous system immunoreactivity, a condition that implicates the vagus nerve in the manipulation of ghrelin's messages. What seems to be clearer is that intestinal inflammation causes an increase in endogenous ghrelin production. Whether this elevated ghrelin concentration functions therapeutically or not demands further research in experimental colitis as well as in human IBD. In line, the identification of ghrelin in mWAT of IBD patients seems

challenging, if we consider the big amounts of ghrelin that immune cells can produce under stimulation.

Concluding, we could underline that many aspects await future clarification, in particular regarding the exact nature and the exact effect of the above-mentioned hormones in IBD.

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