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Adipokines in the pathogenesis of idiopathic inflammatory bowel disease

Rola adipokin w patogenezie nieswoistych zapaleń jelita grubego

Magdalena Olszanecka-Glinianowicz[1], Gabriela Handzlik-Orlik[2], Bartłomiej Orlik[2], Jerzy Chudek[3]

[1]Health Promotion and Obesity Management Unit, Department of Pathophysiology, Medical University of Silesia, Katowice, Poland
[2]Student Scientific Association at Health Promotion and Obesity Management Unit, Department of Pathophysiology, Medical University of Silesia, Katowice, Poland
[3]Pathophysiology Unit, Department of Pathophysiology, Medical University of Silesia, Katowice, Poland

Abstract

Crohn's disease (CD) and ulcerative colitis (UC) are the two common forms of idiopathic inflammatory bowel disease (IBD). The aetiology and pathogenesis of IBD are not yet known. Genetic predisposition has been suggested as playing a role in the improper immune response to commensal microbiota. The main link of IBD pathogenesis is an intestinal immune system disability after enteric infection, resulting in an uncontrolled and chronic inflammatory state.

Recently, numerous studies have been focused on the role of proinflammatory cytokines as well as hormones of adipose tissue named adipokines in the pathogenesis of IBD. Adipokines have pro- and anti-inflammatory properties and can modulate the immune response. It has been shown that obesity is associated with systemic microinflammation. On the other hand, experimental studies have revealed a link between levels of some adipokines and the severity of inflammation in IBD independent of body mass. The fat deposits called 'wrapping' or 'creeping' fat envelop the intestine, and adipokines produced by this tissue play an important role in the pathogenesis of IBD.

The aim of this manuscript was to review the current literature concerning the role of adipokines in the pathogenesis of IBD. **(Endokrynol Pol 2013; 64 (3): 226–231)**

Key words: *leptin, adiponectin, resistin, visfatin, TNF-α, IL-6 Crohn's disease, ulcerative colitis*

Streszczenie

Choroba Crona (CD) i wrzodziejące zapalenie jelit są najczęściej występującymi postaciami nieswoistych zapaleń jelit. Ich etiologia i patogeneza dotychczas nie zostały wyjaśnione. Sugeruje się, że przewlekły stan zapalny jelit jest wynikiem predyspozycji genetycznych i indywidualnej nadmiernej reakcji układu immunologicznego na antygeny fizjologicznej mikroflory jelitowej. Uważa się, że naruszenie równowagi jelitowego układu immunologicznego jest spowodowane infekcją jelitową, która prowadzi do zmian w składzie fizjologicznej mikroflory jelitowej. Bierze się także pod uwagę takie czynniki, jak pochodzenie geograficzne i etniczne oraz styl życia. W ostatnich latach liczne badania oceniały rolę cytokin prozapalnych i hormonów tkanki tłuszczowej nazywanych adipokinami w patogenezie nieswoistych zapaleń jelit. Adipokiny wykazują zarówno pro-, jak i przeciw- zapalne działania i mogą uczestniczyć w regulacji odpowiedzi immunologicznej. Wykazano także, że otyłość wiąże się z przewlekłym układowym stanem zapalnym. Z drugiej strony wyniki badań eksperymentalnych ujawniły związek między stężeniem krążących adipokin a nasileniem procesu zapalnego w jelicie niezależnie od masy ciała. Wydaje się, że istotną rolę w wytwarzaniu adipokin uczestniczących w patogenezie nieswoistego zapalenia jelita odgrywa depozyt tłuszczu zlokalizowany w krezce jelita i bezpośrednio je otaczający.

Celem prezentowanej pracy był przegląd aktualnej literatury dotyczącej roli adipokin w patogenezie nieswoistych zapaleń jelit, takich jak choroba Crona i wrzodziejące zapalenie jelita grubego. **(Endokrynol Pol 2013; 64 (3): 226–231)**

Słowa kluczowe: *leptyna, adiponektyna, rezystyna, wisfatyna, TNF-α, IL-6, choroba Crona, wrzodziejące zapalenie jelita grubego*

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two common forms of idiopathic inflammatory bowel disease (IBD). The aetiology and pathogenesis of both IBD forms are not yet known. It has been suggested that chronic inflammation of the bowel is the result of genetic predisposition and improper immune response to gut commensal microbiota [1]. The importance of genetic predisposition in the pathogenesis of IBD is confirmed by the results described in its higher prevalence in Ashkenazi Jews and first-degree relatives of patients diagnosed with IBD [2]. Moreover, at least nine distinct chromosomal regions loci variants related to IBD have been identified [3, 4]. Additionally, the role of lifestyle in the development of IBD has also been shown [5]. However, the main link of IBD pathogenesis seems to be disability of intestinal immune system after

Prof. Magdalena Olszanecka-Glinianowicz M.D., Ph.D., Health Promotion and Obesity Management Unit, Department of Pathophysiology, Medical University of Silesia, Medyków St. 18, 40–752 Katowice, Poland, tel./fax: + 48 32 252 60 91, e-mail: magols@esculap.pl

enteric infection, resulting in changes of gut commensal microbiota composition as well as an uncontrolled and chronic inflammatory state. So far no specific microorganism involved in the pathogenesis of IBD has been identified. Therefore, it has been hypothesised that disturbed gut microbiota composition rather than a specific pathogen play a role in the pathogenesis of IBD [6]. The additional known factors, modulating immune system activation and affecting the development of IBD, include use of non-steroidal anti-inflammatory drugs [7], smoking [8], and recent appendectomy [9]. It should be emphasised that smoking is a risk factor for CD [10], while in UC it decreases the severity of inflammation [11, 12]. Recently, numerous studies have been focused on the role of proinflammatory cytokines as well as adipose tissue hormones (adipokines) in the pathogenesis of IBD. It has been shown that obesity *per se* is associated with systemic microinflammation, and disturbed circulating adipokines levels [13, 14]. Additionally, the results of experimental studies revealed a link, independent of body mass, between plasma levels of adipokines and severity of colitis [15]. In rats, increased mesenteric fat deposit has been observed during experimental colitis, despite a reduction of body mass and enhanced release of TNF-α and leptin by mesenteric and perinodal adipose tissue [30]. Thus, the adipokines produced by these fat deposits called 'wrapping' or 'creeping' fat enveloping the intestine seem to play an important role in the pathogenesis of IBD [15, 16].

This study reviews the literature concerning the role of adipokines in the pathogenesis of IBD such as Crohn's disease and ulcerative colitis.

Leptin

Leptin is a 16kDa polypeptide hormone produced predominantly by the subcutaneous white adipose tissue (sWAT) [17]. The circulating leptin level is proportional to body mass index (BMI) and fat mass [18]. Leptin is known as a peripheral signal of satiety [9, 19, 20]. Its other biological activities include regulation of hematopoietic, angiogenesis, reproduction and hypothalamic-pituitary-adrenal axis activation [20–23]. Moreover, leptin has proinflammatory properties. Increased circulating leptin level has been observed in infectious and inflammatory diseases [24, 25]. This adipokine stimulates TNF-α and IL-6 production, increases iNOS activity and the secretion of nitric oxide (NO), activates synthesis of leukotriene by monocytes and macrophages, and modulates function of CD4+ T lymphocytes [18, 26]. This suggests that leptin plays an important role in immunity, influencing the function of immune cells by the regulation of cytokine production and polarising T helper cells toward Th1 (long isoform of leptin receptor is expressed on T lymphocytes) [24].

Experimental studies have revealed that leptin modulates intestinal inflammation [27, 28]. It has been shown that leptin-deficient mice are protected from inflammation in some models of IBD [29], whereas, in a rat experimental model of intestinal inflammation, elevated plasma leptin level was observed, regardless of inflammation severity and nutritional status [30]. Overexpression of leptin mRNA in mesenteric visceral adipose tissue (mWAT) has also been found in IBD subjects, [31, 32], contrary to the suppression of leptin secretion by cultured differentiated human adipocytes in chronic inflammatory conditions [32]. The response of colonic cells to inflammation includes leptin release into the gut lumen which exacerbates the epithelial damage and neutrophil infiltration. Therefore, luminal concentrations of leptin are significantly higher in patients with active IBD than in normal colonic luminal fluid [33]. The studies exploring plasma leptin level in IBD have revealed conflicting results. Its levels have been found to be increased [34], unaffected [35], and even decreased [36]. Additionally, infiximab therapy in patients diagnosed with IBD increases circulating leptin level [37]. Larger studies in humans are necessary to clarify the role of leptin in the pathogenesis of IBD.

Potentially, increased circulating leptin, as well as other proinflammatory cytokines, may increase satiety and decrease food intake in IBD subjects, leading to the development of malnutrition. On the other hand, a high leptin level may improve nutrient absorption. It has been shown that leptin may stimulate nutrient absorption by long isoform of its receptor (OB-Rb) localised in brush border or basolateral membrane of enterocytes [38].

An important limitation of the performed studies, and perhaps the cause of conflicting results, is the lack of nutritional status assessment in IBD subjects. Therefore, more detailed studies are necessary to clarify the potential role of leptin in the pathogenesis of IBD.

Adiponectin

Adiponectin is a 244-amino acid protein, produced predominantly by WAT. The monomeric form (30kDa) as well as oligomeric complexes - low molecular weight (LMW) trimers, middle molecular weight (MMW) hexamers, and high molecular weight (HMW) multimers, of adiponectin seem to be secreted only by adipocytes. It has been suggested that HMW is the most important biologically active adiponectin form [39].

Low plasma adiponectin level has been shown in obesity, type 2 diabetes, dyslipidemia and hypertension [40–42], while increased adiponectin levels have

been observed in patients with anorexia nervosa and in fasting healthy subjects [43].

Adiponectin has anti-inflammatory properties. It reduces the release of proinflammatory cytokines such as TNF-α and IL-6 and induces secretion of anti-inflammatory factors (IL-10 and IL-1-receptor antagonist), by macrophages and lymphocytes [44, 45]. Moreover, this adipokine inhibits expression of adhesion molecules (vascular cell adhesion molecule-1, E-selectin, intercellular adhesion molecule-1 and IL-8) in endothelial cells [46–48]. However, some investigators suggest that the HMV adiponectin and its globular domain have proinflammatory properties and participate in NFκB activation [49]. Furthermore, elevated plasma adiponectin level has been found in autoimmune diseases such as rheumatoid arthritis [50].

The dual role of adiponectin in IBD has also been shown in experimental studies. Adiponectin-knockout mice (APN-KO) were developing much more severe colitis, that was attenuated by supplementation of adiponectin, probably by the inhibition of LPS-induced IL-8 production in intestinal epithelial cells [51]. On the other hand, adiponectin-deficient mice were protected from chemically induced colitis, and the administration of adiponectin restored inflammation by the increase of proinflammatory cytokines production and inhibition of growth factor activity [52].

In humans, tissue concentration of adiponectin in hypertrophic mesenteric adipose tissue and its release were significantly higher in subjects with CD than UC [53]. However, the results of studies assessing the circulating adiponectin level in IBD subjects are inconclusive. Both elevated [36] and decreased [35] adiponectin levels in IBD have been observed. Moreover, a higher adiponectin level in UC and lower in CD in women, but not in men, has been found [54]. Therefore, gender-related differences in adiponectin action in IBD have been suggested. Moreover, some authors have suggested that circulating adiponectin may be a risk factor for the occurrence of glucocorticoid-related side effects in children and adolescents with IBD [55].

To clarify the role of adiponectin in the pathogenesis of IBD, further experimental and clinical studies are necessary, especially concerning the association between plasma adiponectin levels, IBD and nutritional status as well as fat deposits.

Resistin

Resistin is a 12.5-kDa member of the cysteine-rich proteins family, cloned in 2001 as a thiazolidinedione-regulated cytokine expressed in rodent adipose tissue. It was initially described as an adipocyte-derived mediator of hepatic insulin resistance [56]. When translating the role of resistin from animals to humans, the interspecies differences have to be taken into consideration. The main source of circulating resistin in animals and in humans is different. In animals, resistin is mainly produced by visceral adipocytes [57], while in humans it is by mononuclear cells [58]. Human visceral adipose tissue (predominantly macrophages) produces only a small part of circulating resistin [59]. Additionally, mouse and human resistin demonstrates only 64.4% mRNA sequence and 59% amino acids homology [60]. This suggests that the physiological function of resistin is different in animals and humans [61]. Numerous studies have revealed that in humans resistin has proinflammatory properties. This protein activates NF-κB signalling pathway and induces production of IL-6, IL-1β and TNF-α by monocytes [57, 61]. Other potential but little known functions of resistin are regulation of metabolic processes and adipogenesis [62]. The proinflammatory action of resistin has been confirmed by clinical studies that have revealed the increased level of this protein in rheumatoid arthritis and IBD [63-66]. It has also been shown that resistin production in mWAT is significantly greater in CD than in subjects with colon cancer. Additionally, plasma resistin level in CD and UC patients was increased, independently of the disease severity [36]. Additionally, the increased circulating resistin level in subjects with active IBD but not during remission was found [35]. This suggests the role of resistin in the inflammation process in IBD.

Visfatin

Visfatin is an adipokine originally identified in visceral adipose tissue. The structure of visfatin is identical to pre-B-cell colony-enhancing factor (PBEF). An experimental study revealed the insulin-mimetic properties of visfatin. It was shown that *in vitro* visfatin enhances glucose uptake by adipocytes and myocytes and inhibits glucose release by hepatocytes [47]. We have recently described a higher circulating visfatin level in obese compared to normal weight women [67]. WAT-derived macrophages and stromal vasculature, rather than adipocytes, are the main source of circulating visfatin [68, 69]. It has been suggested that visfatin is a proinflammatory marker of adipose tissue resident macrophages. Numerous studies have confirmed this hypothesis. Density of resident macrophages in adipose tissue in obese subjects has been shown to be increased. Moreover, both plasma visfatin and TNF-α levels increase with BMI, and correlate with each other [70].

Visfatin stimulates production of matrix-metalloproteinase-9 by monocytes and proinflammatory cytokines, such as TNF-α, IL-6 and IL-8 by peripheral blood mononuclear cells [71, 72]. Increased expression

of visfatin in peripheral blood mononuclear cells has also been shown in rheumatoid arthritis [64], acute lung injury [73] and psoriasis [74].

Recently elevated plasma visfatin level has also been observed in subjects diagnosed with IBD. In CD subjects, increased circulating visfatin concentration was observed independent of the disease severity, while in UC subjects visfatin level was related to severity of inflammation. The expression of visfatin was localised to macrophages, epithelial and dendritic cells within mucosa membrane of IBD patients [75].

Additionally, visfatin has been found to be a causative factor of decreased bone mass density (BMD) in IBD subjects [76].

Thus, visfatin seems to be a link in the pathogenesis of IBD and may play a role in the development of IBD complications such as secondary osteoporosis.

Interleukin 6 (IL-6)

Interleukin 6 is a cytokine produced by numerous cells, including fibroblasts, monocytes, macrophages, endothelial cells and adipocytes. Adipose tissue, especially visceral fat, is a significant source of circulating IL-6 (30%) [77]. In obese subjects, an increasing, proportional to BMI, circulating IL-6 level has been shown [78–80].

Experimental studies have revealed that IL-6 plays an important role in the development of insulin resistance by the inducing the suppression of cytokine signalling-3 pathway [81] and stimulating C-reactive protein (CRP) production by hepatocytes [82]. Additionally, IL-6 stimulates hematopoiesis, maturation of B-cells, T-cell growth, as well as differentiation of neurons [82].

Increased concentration of IL-6 in samples collected from both peripheral and mesenteric veins in subjects with active CD, but not with UC, has been shown. It has been suggested that peripheral blood mononuclear cells, endothelial cells and fibroblasts are the main source of circulating IL-6 in CD subjects [83]. In other studies, increased IL-6 level and its relation to disease severity in CD subjects has been found [84, 85]. Therefore, potentially, IL-6 could be a useful marker in the differentiation of CD and UC, and clinical monitoring of CD severity [86, 87]. However, contradictory results have also been published, showing that secretion of IL-6 in mesenteric fat tissue did not differ in subjects with CD, colon cancer and diverticulitis [53, 65]. Finally, large clinical trials have not confirmed the usefulness of IL-6 assessment in CD [88]. Therefore, it seems that elevated circulating IL-6 level may reflect systemic chronic inflammation accompanying IBD.

Tumour necrosis factor-alpha (TNF-α)

Tumour necrosis factor-α is a proinflammatory cytokine produced mainly by macrophages, lymphocytes and in low quantities by human adipocytes [89]. TNF-α directly and indirectly participates in the inflammatory process through recruitment and activation of inflammatory cells. TNF-α interferes also with other cytokines in inflammation and induces catabolism [90], by stimulation of lipoprotein lipase activity and insulin resistance development [91].

Taking into account everything described above, the question arises concerning the participation of adipocyte-derived TNF-α in a chronic inflammation disease, such as IBD. Desreumaux et al. [92] revealed especially elevated secretion of TNF-α from mesenteric adipocytes. It has been suggested that TNF-α synthesis by mesentery adipose tissue is causally linked to the specific location of mucosal ulcerations [93]. Moreover, Gambero et al. [16] in experimental colitis observed its increased production in mesenteric, especially by perinodal, adipose tissue, and this may explain high basal mesenteric lipolytic activity. Elevated TNF-α production by intestinal mucosa in CD patients has also been shown [94]. Tumour necrosis factor-α activates endothelial cells, induces chemokines secretion and recruits neutrophils in gut mucosa [95]. In Crohn's disease, elevated TNF-α level increases leptin mRNA expression in adipocytes [96, 97]. Kohut et al. [85] suggested that circulating TNF-α level may be a marker distinguishing patients with and without Crohn's disease. The important role of TNF-α in the pathogenesis of CD is confirmed by the effectiveness of therapy with anti-TNF-α drugs in this disease [98].

An increased TNF-α level in the plasma, colonic tissue and stool of UC subjects has also been observed [99]. However, no studies have assessed TNF-α production by intestinal mucosa and perinodal mesenteric adipose tissue in UC patients.

Is obesity a risk factor for inflammatory bowel diseases?

Crohn's disease and ulcerative colitis generally occur more frequently in obese than in normal weight and underweight subjects. Therefore, some researchers have hypothesised that obesity may participate in the pathogenesis of IBD and influence its severity [100, 101]. The data obtained by Mendall et al. [101] revealed a higher frequency of obesity in patients with CD than ulcerative colitis and healthy controls. A correlation between BMI and risk for CD development has also been shown. Further studies have revealed that the activity of CD is more severe in obese than in non-obese subjects

[100]. Contradictory data concerning the frequency of obesity in IBD was obtained in a paediatric population. In children newly-diagnosed with IBD, the prevalence of overweight and obesity was higher in UC than CD subjects (30% *v*. 20%) [102, 103]. However, the association between obesity and severity of the disease (higher rates of IBD-related surgery interventions) was found only in CD children [102].

The results of the few studies published so far, as well as the above described data, suggest that adipokines are the link between obesity and IBD.

Summary

Disturbances in hormonal function of adipose tissue in obesity seem to modulate immune activity and participate in the pathogenesis as well as the course of IBD. However, further studies are necessary to clarify the role of visceral and mesenteric adipose tissue and more precisely describe the links between obesity and IBD development.

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