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Review article

Common links between metabolic syndrome and inflammatory bowel disease: Current overview and future perspectives

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ABSTRACT

Metabolic syndrome (MS) features a constellation of central obesity, dyslipidemia, impaired glucose metabolism and often hypertension joined by insulin resistance and chronic inflammation. All these elements greatly raise patient's risk of cardiovascular disease and type 2 diabetes, resulting in an increased mortality. Metabolic syndrome affects approximately 20–25% of the world's adult population and thus it is essential to study its pathophysiology and seek new pharmacological targets. There is a thoroughly studied link between MS and inflammatory diseases of the gastrointestinal (GI) system, i.e. steatohepatitis. However, recent findings also indicate similarities in pathophysiological features between MS and inflammatory bowel disease (IBD), including adipose tissue dysregulation, inadequate immune response, and inflammation. In this review we aim to outline the pathophysiology of MS and emphasize the aspects revealed recently, such as mineralocorticoid activity, involvement of sex hormones and an accompanying increase in prolactin secretion. More importantly, we focus on the common links between MS and IBD. Finally, we describe new strategies and drug targets that may be utilized in MS therapy, namely adiponectin mimetics, GLP-1-based multi agonists, ABCA1 agonists and possible role of miRNA. We also discuss the possible utility of selected agents as adjuvants in IBD therapy.

Contents

Abbreviations: ABCA1, ATP-binding cassette transporter 1; ABCG1, ATP Binding Cassette G1; AMPK, 5′AMP-activated protein kinase; AP-1, activator protein 1; apo A-I, apolipoproteins A-I; AT, adipose tissue; CCK-1, cholecystokinin; CD, Crohn's disease; CVD, cardiovascular disease; DM2, diabetes mellitus type 2; DPP-IV, dipeptidyl peptidase IV; FABPs, fatty acid binding proteins; FAMP5, Fukuoka Apolipoprotein A-I Mimetic Peptide 5; FGF, fibroblast growth factor; GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like-peptide 1; HbA1c, glycated hemoglobin; HLA, human leukocyte antigens; I1R, type 1 imidazoline receptor; IBD, inflammatory bowel disease; IDF, International Diabetic Federation; IGF1R, insulin-like growth factor 1 receptor; IL-6, interleukin 6; INSR, insulin receptor; LPL, lipoprotein lipase; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein 1; MEDA, deep mesenteric estrogen-regulated genes; miRNA, micro RNA; MR, mineralocorticoid receptors; MS, metabolic syndrome; NF-κB, nuclear factor κβ; NOD2, Nucleotide-Binding Oligomerization Domain Containing 2; NRF-1, nuclear respiratory factor 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPARγ, peroxisome proliferator-activated receptor gamma; RAA, renin-angiotensin-aldosterone system; SIRT4, sirtuin 4; SNPs, single nucleotide polymorphisms; SR-BI, scavenger Receptor Class B type I; SREBP, sterol regulatory element-binding protein TNF-α tumor necrosis factor α; UC, ulcerative colitis; VAT, visceral adipose tissue; VCAM-1, vascular cell adhesion molecule 1.

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Introduction

It is hard to treat "the risk" – and it may be the reason why metabolic syndrome (MS) eludes most attempts at therapy. MS is defined as a constellation of five cardiovascular risk factors: obesity, insulin resistance, hypertension, and dyslipidemia, including hypertriglyceridemia [1]. Each of these disorders adds to mortality, but also – clustered or not – raises the risk of heart attack, stroke and type 2 diabetes mellitus (DM2) and drives the world's cardiovascular disease (CVD) epidemic. Based on ATPIII criteria, MS affects approximately 35% of US adult population [2,3], whereas International Diabetes Federation (IDF) estimates its worldwide prevalence at 25% [3].

There is a well-established link between MS and inflammatory diseases of the gastrointestinal (GI) system, i.e. nonalcoholic fatty liver disease (also known as steatohepatitis). Steatohepatitis increases the risk of DM2 and MS [4,5]; the occurrence of steatohepatitis in MS patients is staggering at 80–85% [5–7]. More recent findings also indicate similarities in pathophysiological features between MS and inflammatory bowel diseases (IBD), defined as either Crohn's disease (CD) or ulcerative colitis (UC). Their prevalence in MS patients is not well-established [8,9], but the presence of MS has been shown to increase the rate of hospitalizations in patients with CD [10].

This paper aims to outline the pathophysiology of MS and highlight a few aspects recently revealed that deserve further attention, including the association between MS and IBD. Among others, we focus on the current therapy trends and ponder the challenges they face. We also put a spotlight on the potential of modern medicine to combat MS and discuss new strategies, drug targets and metabolic pathways that can be utilized against this vicious foe.

Pathophysiology of MS

Course of development

The adipose tissue (AT), and particularly the visceral adipose tissue (VAT) seems to be the central player in the pathophysiology of MS. Recently it has been shown that AT not only stores fatty acids, but it is also a signaling center responsible for the body's energy balance [11]. When faced with an excessive calories uptake, adipocytes become hypertrophic, what leads to central obesity. If this state continues and exceeds their buffer capacity, adipocytes come under oxidative stress and fall into chaos. This results in abnormal levels of adipokines produced by AT, namely upregulation of resistin, leptin, vaspin, visfatin, apelin, and chemerin, and downregulation of adiponectin, zinc-a2-glycopotein, and omentin [12–14]. Some of these hormones have positive, protective effect (leptin, omentin, adiponectin, vaspin, visfatin, and apelin) and will counteract the pathophysiological changes. Others, like resistin, drive the imbalance further and deregulate systemic signaling. For example, obesity is usually coupled with an increased resistance of central nervous system to leptin which leads to hyperleptinemia and reduces leptin's anti-obesity effects [15]. Worse still, hypertrophic adipocytes secrete interleukin 6 (IL-6), tumor necrosis factor α (TNF-α) and monocyte chemoattractant protein 1 (MCP-1), which tips the scale in favor of inflammation [16–18]. Consequently, the tissue recruits monocytes and promotes their differentiation into proinflammatory (M1) macrophages. M1 infiltrate the VAT and integrate their signaling pathways with adipocytes thus propelling chronic, low-grade inflammation. The most aggravating seem to be the macrophages surrounding necrotic adipocytes in so called "crown-like structures". This population, marked as CD-11c+ CD206+ expresses very high levels of integrins and proinflammatory cytokines [18]. In effect, the patient develops insulin resistance driven by lipid accumulation and lipotoxicity, inflammatory signaling (cytokines, adipokines) and transcriptional factors such as nuclear factor κβ (NF-κB) and activator protein 1 (AP-1) [19].

Unifying theories

The process of uncovering, one by one, the details of MS pathophysiology and setting them into a coherent theory has been a painstakingly long one. Hotamisligil et al. [20] investigated the relations between obesity and inflammation and emphasized the role of endoplasmatic reticulum stress response to the energy surplus [21]. The same group also examined the role of fatty acid binding proteins (FABPs), which participate in lipid-mediated signal transduction and integrate lipid metabolism into MS pathophysiological picture [22]. However, these generalizations still fail to ultimately find the cause of MS and explain why some obese individuals do not develop the syndrome. This gap has been filled by Cani's group [23], indicating the microbiome as an additional player, which orchestrates immune and metabolic interactions in obesity, insulin resistance and DM2 [23,24]. The detailed interplay between microbiota and host's physiology is beyond the scope of this review and has been already covered by others (for up-to-date findings see [25]).

Mineralocorticoid receptors

Mineralocorticoids play an important role in AT physiology and the activation of mineralocorticoid receptors (MR) may contribute

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