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Inflammatory Pathways in Metabolic Syndrome: Crosstalk Between Adipose Tissue, Liver, and Gut Microbiota

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ABSTRACT

Metabolic syndrome (MetS) is a multifactorial disorder characterized by central obesity, insulin resistance, hypertension, and dyslipidemia, all of which are closely tied to chronic low-grade inflammation. Emerging evidence reveals a complex interplay between adipose tissue, the liver, and the gut microbiota that sustains this inflammatory milieu. Adipose tissue acts as an active endocrine organ that releases pro-inflammatory adipokines, such as TNF-α and IL-6, which impair insulin signaling and promote hepatic steatosis. In parallel, liver inflammation is fueled by lipid accumulation and innate immune activation through pathways including NF-κB and JNK. Furthermore, gut microbiota dysbiosis exacerbates systemic inflammation by increasing intestinal permeability, leading to endotoxemia driven by lipopolysaccharide (LPS) translocation. This review comprehensively explores the bidirectional inflammatory communication among adipose tissue, liver, and gut, with a focus on the molecular mediators and signaling pathways such as TLR4, NLRP3 inflammasome, and cytokine cascades. We also examine the implications of this inter-organ crosstalk for the progression of metabolic diseases and discuss emerging therapeutic interventions targeting inflammatory axes within this triad.

Keywords: Metabolic syndrome; Inflammation; Adipose tissue; Gut microbiota; Liver

INTRODUCTION

Metabolic syndrome (MetS) is a multifactorial clinical condition that encompasses a cluster of metabolic abnormalities, including central obesity, insulin resistance, dyslipidemia, hypertension, and impaired glucose tolerance [1]. It affects an estimated one-quarter of the global adult population and represents a major public health concern due to its association with significantly increased risk for type 2 diabetes mellitus (T2DM), atherosclerotic cardiovascular disease (ASCVD), and non-alcoholic fatty liver disease (NAFLD) [2]. The pathophysiology of MetS has traditionally been attributed to metabolic dysregulation; however, emerging evidence places chronic low-grade inflammation at the center of disease progression and inter-organ communication [3]. This inflammatory response is not a mere byproduct of metabolic dysfunction; rather, it acts as a central pathogenic mechanism that links adipose tissue dysfunction, hepatic stress, and gut microbial imbalance [4,5]. The interplay among these organs—collectively referred to as the "metabolic-inflammatory axis"—illustrates a complex crosstalk where immune cells, cytokines, adipokines, microbial products, and metabolic signals interact to exacerbate systemic inflammation [6]. Adipose tissue, once considered inert, is now recognized as a critical immune organ, especially in the context of obesity. It secretes a wide array of pro-inflammatory and anti-inflammatory adipokines that influence local and systemic immune responses [7]. The liver, as a central metabolic hub, is susceptible to the spillover effects of adipose inflammation, particularly through the portal vein. It acts both as a target of inflammatory damage and as an amplifier, generating acute-phase proteins and perpetuating systemic immune activation. Meanwhile, the gastrointestinal tract, particularly the gut microbiota, plays a crucial regulatory role in metabolic homeostasis [8,9]. Dysbiosis—an imbalance in microbial composition—leads to increased gut permeability ("leaky gut"), enabling translocation of lipopolysaccharides (LPS) and other pathogen-associated molecular patterns (PAMPs) into the circulation, which further exacerbate hepatic and adipose inflammation [10,11]. This review aims to explore the intricate molecular and cellular mechanisms underlying inflammatory crosstalk among the adipose tissue, liver, and gut microbiota in metabolic syndrome. A comprehensive understanding of this tripartite interaction offers valuable

insights into the development of novel anti-inflammatory and immunomodulatory therapies targeting the root causes of metabolic dysfunction.

Inflammation in Adipose Tissue: The Initiator

Adipose tissue plays a pivotal role in energy homeostasis and endocrine signaling [12]. However, in the context of obesity, a core feature of MetS, it becomes a primary instigator of systemic inflammation. As adipocytes expand, they outgrow their vascular supply, leading to hypoxia, oxidative stress, and cell death [13]. These stress signals initiate the secretion of pro-inflammatory adipokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), while levels of the anti-inflammatory adipokine adiponectin decline markedly [14]. This altered secretory profile creates a local inflammatory environment that attracts immune cells, particularly monocytes, which differentiate into macrophages. The infiltration of macrophages into adipose tissue is a hallmark of obesity-induced inflammation. In lean adipose tissue, macrophages typically adopt an anti-inflammatory M2 phenotype that supports tissue homeostasis. However, in obese individuals, these macrophages shift to a pro-inflammatory M1 phenotype, characterized by the production of nitric oxide, TNF-α, and IL-1β [15]. This phenotypic switch is driven by metabolic stress and cytokine signaling, particularly through Toll-like receptors (TLRs) and the nuclear factor-kappa B (NF-κB) and c-Jun N-terminal kinase (JNK) pathways.

The chronic inflammatory milieu disrupts insulin signaling via serine phosphorylation of insulin receptor substrate (IRS) proteins, contributing to systemic insulin resistance, a key feature of MetS [16]. Additionally, hypertrophic adipocytes release extracellular vesicles containing miRNAs and inflammatory mediators that communicate with distant organs, including the liver and gut, thereby amplifying systemic inflammation. Moreover, dysfunctional adipose tissue also promotes ectopic fat deposition in non-adipose organs like the liver and muscle, compounding insulin resistance [17]. The adipose tissue-liver axis is especially significant, as pro-inflammatory mediators and free fatty acids (FFAs) are transported directly to the liver via the portal circulation. This "portal theory" explains how visceral fat contributes disproportionately to hepatic steatosis and inflammation. Collectively, the inflammation originating in adipose tissue sets the stage for a cascade of immune-metabolic disturbances that influence other organs, positioning it as a crucial therapeutic target in managing MetS [18].

Hepatic Inflammation and Immune Activation

The liver is not only a metabolic powerhouse but also an immunological organ, containing the largest population of resident macrophages—Kupffer cells—in the body. It acts as a critical interface between the gastrointestinal tract and systemic circulation. In MetS, the liver becomes a site of immune activation due to continuous exposure to inflammatory signals from adipose tissue and gut-derived endotoxins [19]. One of the primary insults is the influx of free fatty acids (FFAs) from hypertrophic adipocytes and increased de novo lipogenesis. Excess FFAs lead to hepatic steatosis and mitochondrial dysfunction, resulting in the generation of reactive oxygen species (ROS) and lipid peroxidation products, which cause hepatocellular injury [20]. Damaged hepatocytes release damage-associated molecular patterns (DAMPs) that activate Kupffer cells and hepatic stellate cells (HSCs) [21]. These cells, through TLR4 and NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome pathways, produce pro-inflammatory cytokines such as IL-1β, IL-18, and TNF-α, thereby driving the transition from simple steatosis to non-alcoholic steatohepatitis (NASH) [22] In parallel, the liver produces acute-phase proteins such as C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen in response to IL-6 and other systemic cytokines. These proteins act as amplifiers of inflammation and serve as biomarkers of metabolic dysfunction and cardiovascular risk [23]. The hepatic immune environment becomes increasingly pro-inflammatory, with the recruitment of neutrophils, monocyte-derived macrophages, and cytotoxic T cells, contributing to chronic liver injury and fibrosis.

Another key aspect is the liver's role in lipid and glucose metabolism. Inflammatory signaling through NF-κB and JNK impairs insulin receptor signaling, exacerbating hepatic insulin resistance [24]. This leads to increased hepatic glucose production and worsens hyperglycemia in MetS patients. Moreover, dysregulated cholesterol metabolism and very low-density lipoprotein (VLDL) secretion contribute to the development of atherogenic dyslipidemia.

The liver's bidirectional communication with the gut via the portal vein makes it especially susceptible to microbial products such as LPS, which leak into the circulation due to increased gut permeability in MetS [19]. These endotoxins further activate hepatic TLR4 signaling, perpetuating inflammation. In summary, hepatic inflammation is both a consequence of upstream adipose tissue dysfunction and a driver of systemic metabolic deterioration [25]. Understanding its immunometabolic mechanisms is critical to developing targeted therapies for MetS and its complications.

Gut Microbiota Dysbiosis and Intestinal Inflammation

The gut microbiota plays a crucial role in maintaining metabolic and immune homeostasis. In individuals with metabolic syndrome (MetS), the microbial landscape is profoundly altered—a phenomenon known as dysbiosis [26]. One of the most consistent observations in MetS is an increased Firmicutes-to-Bacteroidetes ratio, which is

associated with enhanced energy harvest from the diet, increased fat storage, and promotion of low-grade inflammation. This dysbiotic shift is also accompanied by a reduction in microbial diversity and a decline in beneficial bacterial species such as Faecalibacterium prausnitzii, Akkermansia muciniphila, and Bifidobacterium species [27].
A critical consequence of dysbiosis is compromised gut barrier function [28]. Normally, intestinal epithelial cells form a tight physical barrier sealed by tight junction proteins, such as occludin and claudin. In MetS, this barrier becomes "leaky," due to microbial imbalance and reduced production of protective metabolites like butyrate [18]. This loss of integrity permits the translocation of microbial products including lipopolysaccharides (LPS), flagellin, and peptidoglycan—into the systemic circulation [28]. These pathogen-associated molecular patterns (PAMPs) activate innate immune receptors, particularly Toll-like receptor 4 (TLR4), on immune cells, hepatocytes, and adipocytes, leading to downstream activation of nuclear factor-kappa B (NF-κB) and the release of pro-inflammatory cytokines [29].
Furthermore, gut dysbiosis leads to a reduction in short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, which are normally produced through microbial fermentation of dietary fibers. SCFAs are vital for maintaining intestinal barrier integrity, regulating immune tolerance, and enhancing insulin sensitivity. Their depletion exacerbates mucosal inflammation and metabolic derangements [24]. Conversely, the abundance of pathogenic metabolites such as trimethylamine N-oxide (TMAO)—a gut-derived metabolite implicated in atherogenesis—increases in MetS, contributing to endothelial dysfunction and cardiovascular risk.
Additionally, alterations in bile acid metabolism occur due to changes in microbial composition. Secondary bile acids modulate inflammation and metabolic function through receptors such as FXR and TGR5 [30]. In dysbiosis, this signaling becomes impaired, further deranging lipid and glucose homeostasis. Thus, gut microbiota dysbiosis not only initiates local inflammation in the intestine but also acts as a systemic amplifier of metabolic inflammation by interacting with hepatic and adipose tissues [31]. Restoring microbial balance is, therefore, a critical therapeutic target in managing MetS and its associated complications.

Molecular Crosstalk Among Adipose Tissue, Liver, and Gut

Metabolic syndrome arises not merely from dysfunction within individual organs but from a tightly regulated and pathological communication network linking the adipose tissue, liver, and gut. This tri-organ axis is governed by a multitude of signaling molecules—including cytokines, adipokines, microbial metabolites, and hormones—that establish a systemic inflammatory loop [5].
Central to this crosstalk is lipopolysaccharide (LPS), a bacterial endotoxin that translocates from the gut into circulation due to increased intestinal permeability [32]. LPS binds to TLR4 on adipocytes, hepatocytes, and immune cells, triggering a cascade of pro-inflammatory responses. This includes the activation of NF-κB and mitogen-activated protein kinase (MAPK) pathways, leading to increased production of cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [33]. These cytokines exert systemic effects, promoting insulin resistance and further disrupting metabolic equilibrium.
Another key player is the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome [34]. It functions as a molecular sensor of metabolic stress—such as lipotoxicity, oxidative stress, and mitochondrial dysfunction—and mediates caspase-1 activation and IL-1β maturation. NLRP3 is active in all three organs and acts as a converging node for sterile inflammation, linking innate immunity to metabolic disease. Adipose-derived hormones such as leptin and resistin, as well as gut-derived hormones like glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), also modulate inflammatory pathways [35]. Leptin, elevated in obesity, acts pro-inflammatory and contributes to hepatic insulin resistance. In contrast, GLP-1 and PYY are anti-inflammatory and enhance insulin sensitivity, but their secretion is blunted in dysbiotic conditions. This molecular dialogue is further modulated by extracellular vesicles and microRNAs (miRNAs), which act as inter-organ messengers. Adipose tissue-derived exosomes, for example, can carry miRNAs that influence hepatic lipid metabolism or gut permeability [36]. Altogether, the molecular crosstalk among adipose tissue, liver, and gut establishes a vicious cycle of metabolic and immune dysregulation, underscoring the need for multi-targeted interventions in the treatment of MetS.

Therapeutic Perspectives and Anti-inflammatory Strategies

Given the multifactorial pathogenesis of MetS, therapeutic strategies must aim at disrupting the inflammatory crosstalk among adipose tissue, liver, and gut. Recent advances suggest a range of pharmacological and non-pharmacological approaches that can alleviate inflammation and restore metabolic homeostasis [18]. Probiotics and Prebiotics: These agents are among the most promising interventions for modulating gut microbiota. Probiotics such as Lactobacillus and Bifidobacterium species restore microbial balance, enhance SCFA production, and strengthen the intestinal barrier [37]. Prebiotics—non-digestible fibers like inulin and fructooligosaccharides—selectively stimulate the growth of beneficial bacteria, indirectly reducing systemic inflammation. Anti-inflammatory Pharmaceuticals: Drugs targeting inflammatory pathways offer another avenue for treatment. NF-κB

and JNK inhibitors are under investigation for their ability to reduce cytokine production and insulin resistance [38]. Biologics targeting IL-1β (e.g., anakinra) have shown promise in reducing inflammation and improving glycemic control in MetS patients. Hormonal Modulators: GLP-1 receptor agonists (e.g., liraglutide, semaglutide) not only enhance insulin secretion and suppress appetite but also exhibit direct anti-inflammatory effects on liver and adipose tissue [39]. Peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists, such as pioglitazone, improve adipocyte function and reduce macrophage infiltration in adipose tissue. Nutraceuticals and Natural Compounds: Polyphenols such as curcumin and resveratrol exhibit potent anti-inflammatory and antioxidant properties [40]. They modulate signaling pathways like NF-κB and NLRP3, improve gut barrier function, and influence microbiota composition. Omega-3 fatty acids have also been shown to reduce hepatic steatosis and systemic inflammation. Lifestyle Interventions: Caloric restriction, increased physical activity, and high-fiber diets have been consistently shown to reduce body weight, improve insulin sensitivity, and lower circulating inflammatory biomarkers [41]. Exercise enhances SCFA production and stimulates myokines that exert systemic anti-inflammatory effects. The therapeutic landscape for MetS is increasingly embracing a multi-organ, systems biology approach that targets the root of inflammation [42]. Personalized and integrative interventions combining diet, pharmacotherapy, and microbiota modulation hold the greatest promise for long-term management and disease reversal.

CONCLUSION

The chronic low-grade inflammation observed in metabolic syndrome is sustained by a coordinated crosstalk among adipose tissue, liver, and gut microbiota. Disrupting the inter-organ inflammatory pathways represents a promising strategy to mitigate the progression of metabolic disorders. Further research into the temporal and spatial regulation of this axis is essential for developing precision therapeutics tailored to metabolic-inflammatory phenotypes.

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