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Adipose Tissue Inflammation in Metabolic Syndrome: Molecular Pathways and Targeted Interventions

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ABSTRACT

Metabolic syndrome (MetS) encompasses a cluster of interrelated metabolic abnormalities, including central obesity, insulin resistance, dyslipidemia, and hypertension. Chronic low-grade inflammation of adipose tissue is now recognized as a central pathogenic driver of MetS. Dysfunctional adipocytes, coupled with immune cell infiltration, especially of pro-inflammatory macrophages, contribute to systemic metabolic disturbances through the release of adipokines, cytokines, and chemokines. Key molecular pathways, including NF-κB, JNK, and NLRP3 inflammasome signaling, orchestrate this inflammatory response. The crosstalk between hypertrophic adipocytes and innate immune cells exacerbates insulin resistance and endothelial dysfunction. Additionally, oxidative stress, endoplasmic reticulum stress, and hypoxia further amplify inflammation. Understanding the cellular and molecular mechanisms underlying adipose tissue inflammation provides a platform for identifying potential therapeutic interventions. Strategies targeting inflammation, such as anti-inflammatory pharmacological agents (e.g., thiazolidinediones, salicylates), lifestyle modifications, bariatric surgery, and novel approaches like miRNA regulation and immunomodulation, offer promising avenues to mitigate MetS progression. This review explores the complex molecular landscape of adipose tissue inflammation and highlights emerging therapeutic strategies aimed at restoring metabolic homeostasis.

Keywords: Adipose tissue, inflammation, metabolic syndrome, insulin resistance, cytokines, NF-κB, JNK, NLRP3 inflammasome, macrophages

INTRODUCTION

Metabolic syndrome (MetS) represents a growing global health concern and is characterized by a cluster of interrelated metabolic abnormalities, including central obesity, insulin resistance, hypertension, dyslipidemia, and glucose intolerance[1–3]. The increasing prevalence of MetS is closely tied to the global surge in obesity, sedentary lifestyles, and unhealthy dietary patterns. At the heart of this syndrome lies a complex interplay of genetic, environmental, and physiological factors, with adipose tissue dysfunction emerging as a central contributor[4–6]. Far from being a passive reservoir for energy storage, adipose tissue is now recognized as a highly active endocrine organ, capable of secreting a wide range of bioactive molecules collectively known as adipokines, that influence systemic metabolism, inflammation, and insulin sensitivity[7, 8].

One of the pivotal pathological features of MetS is chronic low-grade inflammation in adipose tissue. Adipose tissue inflammation is characterized by the infiltration of various immune cells, notably macrophages, T lymphocytes, and mast cells, into adipose depots[9]. These immune cells release a host of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), which exacerbate metabolic dysfunction by impairing insulin signaling pathways[10]. The hypertrophy and hyperplasia of adipocytes in the setting of excessive caloric intake contribute to cellular stress and the activation of inflammatory signaling cascades. This state of inflammation not only disrupts adipokine secretion leading to reduced levels of insulin-sensitizing adiponectin and increased leptin resistance, but also promotes lipolysis and ectopic lipid accumulation in organs such as the liver and skeletal muscle, further impairing insulin action[11, 12]. The cellular and molecular mechanisms underlying adipose tissue inflammation are multifaceted. Adipocytes under metabolic stress release danger-associated molecular patterns (DAMPs), including saturated fatty acids and oxidized lipids, which activate pattern recognition receptors such as Toll-like receptors (TLRs) on immune cells. This leads to the activation of nuclear factor-kappa B (NF-κB) and c-Jun N-terminal kinase (JNK) signaling pathways, culminating in the transcription of pro-inflammatory

genes[13]. Furthermore, macrophages within adipose tissue undergo phenotypic polarization from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 state, amplifying local and systemic inflammation. Crosstalk between immune cells and adipocytes, mediated by chemokines and cytokines, sustains the inflammatory milieu and establishes a feed-forward loop that exacerbates metabolic dysfunction[14]. Given the central role of adipose tissue inflammation in the pathogenesis of MetS, targeted strategies aimed at modulating this process offer promising therapeutic avenues. Lifestyle interventions, including weight loss through dietary modification and regular physical activity, remain foundational and have been shown to reduce adipose inflammation and improve metabolic parameters[15]. Pharmacological agents targeting inflammatory pathways such as inhibitors of TNF-α, IL-1β, and MCP-1 signaling, are under investigation, although their systemic immunosuppressive effects raise safety concerns. Emerging evidence also highlights the role of gut microbiota in modulating adipose tissue inflammation. Dysbiosis, or imbalance in gut microbial composition, can lead to increased intestinal permeability and systemic endotoxemia, further fueling adipose inflammation. Thus, interventions such as prebiotics, probiotics, and fecal microbiota transplantation may hold potential in mitigating inflammatory processes linked to MetS[16]. Moreover, novel therapeutic targets such as adipose tissue-resident regulatory T cells (Tregs), peroxisome proliferator-activated receptors (PPARs), and AMP-activated protein kinase (AMPK) activators are being explored for their capacity to restore adipose tissue homeostasis and resolve inflammation[17]. Advances in nanotechnology and drug delivery systems are also enabling more precise targeting of inflammatory mediators within adipose tissue, minimizing off-target effects. In sum, adipose tissue inflammation plays a pivotal role in the initiation and progression of metabolic syndrome. It bridges the gap between obesity and metabolic dysfunction through a complex network of cellular interactions and inflammatory mediators[18–20]. A deeper understanding of these underlying mechanisms offers critical insights into the development of targeted interventions aimed at reducing the burden of MetS and its associated complications. Continued research in this area is essential for identifying effective strategies to restore metabolic health and combat the global epidemic of obesity-related disorders.

Adipose Tissue as an Endocrine Organ

Adipokines and Inflammatory Balance in Adipose Tissue

Adipose tissue is not merely an energy reservoir but also functions as an active endocrine organ by secreting various bioactive molecules known as adipokines. These adipokines—including leptin, adiponectin, resistin, and visfatin play crucial roles in metabolic homeostasis, appetite regulation, lipid metabolism, and immune responses[15, 21, 22]. Leptin, primarily involved in appetite suppression and energy expenditure, also exhibits pro-inflammatory properties by stimulating cytokine production and immune cell activation[23]. Adiponectin, on the other hand, is known for its anti-inflammatory and insulin-sensitizing effects. It enhances glucose uptake and fatty acid oxidation while inhibiting inflammatory signaling pathways such as NF-κB. In a lean and metabolically healthy state, a harmonious balance between pro- and anti-inflammatory adipokines is maintained, contributing to normal metabolic function[4, 24, 25].

However, in obesity and metabolic syndrome (MetS), this balance is disrupted due to adipocyte hypertrophy and hyperplasia. Enlarged adipocytes exhibit reduced secretion of adiponectin and increased secretion of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1)[26]. These changes create a chronic low-grade inflammatory environment within adipose tissue. Furthermore, elevated free fatty acids (FFAs) released by hypertrophic adipocytes act as ligands for Toll-like receptors on immune cells, further amplifying inflammatory responses. MCP-1, in particular, recruits circulating monocytes into adipose tissue, where they differentiate into pro-inflammatory macrophages, perpetuating inflammation and contributing to systemic insulin resistance[27]. This adipokine imbalance not only affects local tissue homeostasis but also impacts distant organs through endocrine signaling, thereby linking adipose tissue dysfunction to the pathogenesis of type 2 diabetes, cardiovascular disease, and other components of MetS. Understanding the mechanisms that regulate adipokine secretion and function is therefore critical for developing targeted interventions to restore metabolic health[27].

Cellular Drivers of Inflammation in Adipose Tissue

The chronic low-grade inflammation observed in adipose tissue during obesity and metabolic syndrome is orchestrated by a complex interplay of cellular components, predominantly immune cells that infiltrate the tissue in response to metabolic stress[10]. The initial trigger of this inflammatory cascade is often the expansion of adipocytes due to excess nutrient storage. Hypertrophic adipocytes experience hypoxia, endoplasmic reticulum (ER) stress, and oxidative stress, leading to altered secretion of adipokines and increased production of chemokines like monocyte chemoattractant protein-1 (MCP-1). MCP-1 recruits circulating monocytes into the adipose tissue, where they differentiate into classically activated M1 macrophages—key drivers of inflammation[28]. These M1 macrophages accumulate around dead or dying adipocytes, forming "crown-like structures" and secrete high levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6)[29]. These cytokines interfere with insulin receptor signaling, particularly through serine phosphorylation of insulin receptor substrate (IRS) proteins, thus promoting insulin resistance. In addition to macrophages, T lymphocytes play a critical role in modulating inflammation. CD8+ cytotoxic T cells and Th1 CD4+ helper T cells infiltrate adipose tissue early in obesity and contribute to macrophage activation through the secretion of interferon-gamma (IFN-γ)[30]. Conversely,

regulatory T cells (Tregs) are typically reduced in obese adipose tissue, removing an important anti-inflammatory influence[31]. Other immune cells, including B cells, neutrophils, eosinophils, and mast cells, also contribute to the inflammatory milieu. B cells produce pro-inflammatory antibodies and cytokines, while neutrophils secrete elastase and other proteases that damage tissue integrity. Mast cells release histamine and cytokines that further exacerbate inflammation[32]. Together, this network of immune cells sustains a chronic inflammatory environment in adipose tissue, ultimately impairing systemic metabolic function and increasing the risk for insulin resistance, type 2 diabetes, and cardiovascular disease. Targeting these cellular pathways holds therapeutic potential for mitigating obesity-associated metabolic complications.

Molecular Pathways Involved in Adipose Tissue Inflammation

Several key signaling pathways regulate adipose tissue inflammation: **NF-κB Signaling**: The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway plays a central role in mediating inflammatory responses within adipose tissue, particularly in the context of metabolic syndrome and obesity. Under normal conditions, NF-κB remains inactive in the cytoplasm, bound to the inhibitor IκB[33]. However, upon stimulation by free fatty acids (FFAs), inflammatory cytokines such as TNF-α and IL-1β, or through activation of pattern recognition receptors like Toll-like receptors (TLRs), IκB is phosphorylated and degraded, allowing NF-κB to translocate into the nucleus. Once in the nucleus, NF-κB promotes the transcription of a wide range of pro-inflammatory genes, including TNF-α, IL-6, MCP-1, and various chemokines[34]. This results in a cascade of inflammatory events in adipocytes and infiltrating immune cells such as macrophages. In adipose tissue, NF-κB signaling sustains a chronic inflammatory state that disrupts insulin signaling, impairs glucose uptake, and propagates systemic inflammation. Moreover, its activation contributes to the recruitment and polarization of macrophages towards a pro-inflammatory M1 phenotype, further amplifying the inflammatory milieu. Given its pivotal regulatory role, NF-κB is considered a master switch of metabolic inflammation and a potential therapeutic target for mitigating adipose tissue dysfunction and insulin resistance in metabolic disorders[19, 20, 34].

JNK Pathway: The c-Jun N-terminal kinase (JNK) signaling pathway is a crucial mediator of stress-induced inflammation and metabolic dysregulation in adipose tissue. JNK belongs to the mitogen-activated protein kinase (MAPK) family and is activated in response to various cellular stressors, including elevated levels of free fatty acids (FFAs), oxidative stress, and pro-inflammatory cytokines[35]. Upon activation, JNK phosphorylates several downstream targets, including transcription factors such as c-Jun and insulin receptor substrate-1 (IRS-1). Phosphorylation of IRS-1 at serine residues inhibits its activity, thereby impairing insulin receptor signaling and contributing to the development of insulin resistance. In adipocytes and immune cells residing in adipose tissue, activated JNK enhances the expression of inflammatory cytokines such as TNF-α and IL-6, exacerbating the inflammatory environment[35]. This pro-inflammatory loop not only disrupts insulin sensitivity locally but also exerts systemic effects that impair metabolic homeostasis. Chronic JNK activation has been linked to obesity-induced insulin resistance and glucose intolerance in both human and animal models[36]. Furthermore, JNK plays a role in macrophage recruitment and polarization, reinforcing adipose tissue inflammation. Given its dual involvement in both inflammation and insulin resistance, the JNK pathway presents a potential therapeutic target for treating metabolic syndrome and associated pathologies.

NLRP3 Inflammasome: The NLRP3 inflammasome is an intracellular multiprotein complex that serves as a critical sensor of metabolic stress and danger-associated molecular patterns in adipose tissue[37]. Comprising the NLRP3 sensor, ASC adaptor protein, and pro-caspase-1, this inflammasome is activated by stimuli such as mitochondrial dysfunction, excess free fatty acids, ceramides, and reactive oxygen species (ROS). Upon activation, NLRP3 facilitates the autocatalytic cleavage of pro-caspase-1 into active caspase-1, which in turn processes pro-inflammatory cytokines pro-IL-1β and pro-IL-18 into their mature, biologically active forms. IL-1β and IL-18 are central mediators of metabolic inflammation, promoting further immune cell recruitment, adipocyte dysfunction, and systemic insulin resistance. In obesity, persistent NLRP3 activation in adipose tissue macrophages and other immune cells contributes significantly to chronic low-grade inflammation[37]. This inflammasome has also been shown to impair insulin signaling pathways, particularly in the liver and muscle, by enhancing cytokine-mediated inhibition of IRS-1 and IRS-2. Furthermore, NLRP3-driven inflammation exacerbates lipid accumulation and promotes ectopic fat deposition, contributing to organ dysfunction. Targeting the NLRP3 inflammasome offers promising therapeutic potential in metabolic diseases, as evidenced by preclinical studies showing improved insulin sensitivity and reduced inflammation upon genetic or pharmacologic inhibition of this pathway.

ER Stress and Hypoxia: In the setting of obesity, the rapid expansion of adipose tissue often exceeds its vascular supply, leading to localized hypoxia and increased metabolic demand[38]. These conditions induce endoplasmic reticulum (ER) stress, a state where protein folding capacity is overwhelmed due to increased synthesis of inflammatory and metabolic proteins. ER stress activates the unfolded protein response (UPR), which aims to restore homeostasis but can also initiate inflammatory signaling when prolonged or unresolved. This includes the activation of pro-inflammatory transcription factors such as NF-κB and JNK, leading to the upregulation of cytokines like TNF-α, IL-6, and MCP-1[39]. Simultaneously, hypoxia stabilizes hypoxia-inducible factor-1α (HIF-1α), a transcription factor that promotes the expression of genes involved in angiogenesis, glycolysis,

inflammation, and extracellular matrix remodeling. In adipose tissue, HIF-1α also drives the recruitment of inflammatory immune cells and the development of fibrosis, which further impairs adipose function and insulin sensitivity. The interplay between ER stress and hypoxia creates a self-perpetuating cycle of inflammation, cellular dysfunction, and metabolic imbalance[39]. This synergistic effect is central to the pathogenesis of obesity-related insulin resistance and systemic metabolic disturbances. Therapeutic strategies aimed at reducing ER stress or improving oxygen delivery may thus ameliorate adipose inflammation and improve metabolic outcomes.

Systemic Consequences of Adipose Tissue Inflammation: Chronic inflammation in adipose tissue exerts profound effects beyond local dysfunction, playing a central role in the systemic metabolic derangements observed in obesity and metabolic syndrome (MetS). One of the primary systemic consequences is the development of insulin resistance[21, 22]. Pro-inflammatory cytokines such as TNF-α and IL-6 disrupt insulin signaling by promoting the serine phosphorylation of insulin receptor substrates (IRS-1 and IRS-2), thereby impairing downstream signaling pathways essential for glucose uptake and utilization in skeletal muscle, liver, and adipose tissue[40, 41]. This interference reduces glucose transporter-4 (GLUT4) translocation, contributing to hyperglycemia. Additionally, inflammation promotes hepatic gluconeogenesis and inhibits glycogen synthesis, exacerbating insulin resistance. Adipose tissue inflammation also alters lipid metabolism by increasing lipolysis and circulating free fatty acids, which are deposited ectopically in non-adipose tissues like the liver and muscle, further impairing their metabolic function. This lipotoxicity is linked to the development of non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease[4, 5]. Moreover, inflammatory mediators induce endothelial dysfunction, promoting vascular stiffness, hypertension, and atherogenesis. The cumulative effect of these disruptions is an increased risk of type 2 diabetes, cardiovascular disease, and other MetS components. Therefore, targeting adipose tissue inflammation represents a promising strategy for preventing and managing systemic metabolic diseases.

Future Perspectives and Challenges

While significant progress has been made in elucidating the pathways linking adipose inflammation and MetS, translating this knowledge into safe, effective therapies remains challenging. Personalized approaches, considering individual variations in adipose tissue distribution and immune response, are essential. Moreover, targeting inflammation without compromising host defense is a critical concern. Advances in omics technologies and systems biology may enable the identification of new biomarkers and therapeutic targets.

CONCLUSION

Adipose tissue inflammation is a central pathophysiological feature of metabolic syndrome, contributing to insulin resistance, dyslipidemia, and cardiovascular risk. A deeper understanding of the molecular and cellular mechanisms driving this inflammation provides a foundation for developing targeted interventions. Integrative strategies combining lifestyle, pharmacological, and emerging molecular therapies hold promise in attenuating inflammation and restoring metabolic health.

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