Journal of Clinical and Cellular Immunology

OPEN ACCESS Freely available online

Commentary

Immune Dysregulation in Metabolic Syndrome and Obesity

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DESCRIPTION

Metabolic syndrome and obesity are global health challenges with rising prevalence, closely associated with increased risks of type 2 diabetes, cardiovascular diseases, and certain cancers. Beyond their metabolic consequences, these conditions profoundly affect the immune system, leading to chronic low-grade inflammation and immune dysregulation. The interplay between excess adiposity, metabolic stress, and immune function is complex and bidirectional metabolic dysfunction drives immune alterations, while immune dysregulation exacerbates metabolic abnormalities. Understanding this relationship is crucial, as it underpins the development of novel therapeutic approaches aimed at mitigating the chronic inflammation and immune dysfunction associated with obesity and metabolic syndrome.

Obesity-induced immune dysregulation

Obesity is characterized by excessive accumulation of adipose tissue, which is not only an energy storage organ but also an active endocrine and immune organ. Adipose tissue in obese individuals undergoes remodeling, including hypertrophy of adipocytes, hypoxia due to inadequate vascularization, and infiltration of immune cells such as macrophages and T lymphocytes. This leads to a state of chronic low-grade inflammation, often termed "metaflammation," which is distinct from acute inflammation observed during infections.

Macrophages are central players in obesity-associated immune dysregulation. In lean individuals, adipose tissue contains predominantly M2-like anti-inflammatory macrophages that maintain tissue homeostasis. Obesity shifts the macrophage population toward the M1-like pro-inflammatory phenotype, which secretes cytokines such as tumor necrosis factor-alpha, Interleukin-6 (IL-6), and Monocyte Chemoattractant Protein-1 (MCP-1). These inflammatory mediators contribute to insulin resistance by interfering with insulin receptor signaling in adipocytes and other metabolic tissues.

T cells are also dysregulated in obesity. There is an increase in pro-inflammatory Th1 and Th17 cells in adipose tissue, while regulatory T cells (Tregs), which normally suppress inflammation, are reduced. This imbalance favors a pro-inflammatory environment that exacerbates metabolic disturbances. Additionally, B cells in obese adipose tissue produce pathogenic antibodies and secrete pro-inflammatory cytokines, further amplifying the inflammatory milieu. Natural Killer (NK) cells, which play a role in immune surveillance and tissue homeostasis, show impaired cytotoxic activity in obesity, contributing to increased susceptibility to infections and reduced antitumor immunity.

Mechanisms linking metabolic dysfunction to immune alterations

Several mechanisms underlie the immune dysregulation observed in metabolic syndrome and obesity. One key driver is adipose tissue hypoxia. As adipocytes enlarge, oxygen diffusion becomes limited, leading to hypoxia within adipose tissue. Hypoxic conditions stabilize hypoxia-inducible factor-1 alpha, which triggers the expression of pro-inflammatory genes, promotes macrophage recruitment, and disrupts adipocyte function.

Metabolic stress, particularly excess nutrient availability and lipid accumulation, directly affects immune cell metabolism. Obesity-induced lipotoxicity and elevated free fatty acids activate pattern recognition receptors such as Toll-Like Receptor 4 (*TLR4*) on immune cells, inducing inflammatory signaling pathways. These pathways increase cytokine production and promote immune cell infiltration into metabolic tissues. Additionally, Endoplasmic Reticulum (ER) stress in adipocytes and hepatocytes further contributes to inflammation by activating stress response pathways and inflammasomes.

Chronic systemic inflammation associated with obesity also disrupts immune tolerance and adaptive immunity. Persistent exposure to inflammatory mediators can lead to T cell exhaustion, impairing their ability to mount effective responses to pathogens or tumor cells. Similarly, B cell dysfunction can result in aberrant antibody production, increasing the risk of autoimmune phenomena. The dysregulated cross-talk between metabolic and immune pathways creates a vicious cycle inflammation exacerbates insulin resistance and lipid dysregulation, which in turn fuels further immune activation.

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Received: 25-Aug-2025, Manuscript No. JCCI-25-39136;**Editor assigned:**27-Aug-2025, PreQC No. JCCI-25-39136 (PQ); **Reviewed:** 10-Sep-2025, QC No. JCCI-25-39136; **Revised:** 17-Sep-2025, Manuscript No. JCCI-25-39136 (R);**Published:** 24-Sep-2025, DOI: 10.35248/2155-9899.25.16.770

Citation: Hannah M (2025). Immune Dysregulation in Metabolic Syndrome and Obesity. J Clin Cell Immunol. 16:770

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Furthermore, the gut microbiota plays a significant role in immune-metabolic interactions. Obesity and high-fat diets alter the composition and function of gut microbiota, promoting endotoxemia through increased intestinal permeability. Lipopolysaccharide from gram-negative bacteria enters circulation, activating systemic inflammation and contributing to metabolic and immune dysfunction. These gut-derived signals illustrate the complex systemic nature of immune dysregulation in metabolic syndrome.

CONCLUSION

Immune dysregulation is a hallmark of metabolic syndrome and obesity, manifesting as chronic low-grade inflammation, altered immune cell populations, and impaired immune function. Adipose tissue serves as both a source and a target of inflammation, with macrophages, T cells, B cells, and NK cells all contributing to the pro-inflammatory milieu. Mechanisms such as adipose hypoxia, nutrient overload, ER stress, and gut microbiota alterations link metabolic dysfunction to immune disturbances, creating a self-perpetuating cycle of inflammation and metabolic impairment. Recognizing the intricate connection between metabolic and immune pathways has important therapeutic implications. Interventions targeting inflammation, modulating immune cell activity, or restoring metabolic homeostasis could reduce obesity-related complications and improve overall immune competence. Ultimately, addressing immune dysregulation is a critical component in the fight against the growing global burden of obesity and metabolic syndrome.