Mechanisms by Which Obesity Affects Respiratory System Resistance to Infection: Postprint

Authors: Wan Taomei, Gan Linli, Zuo Zhicai, Ren Yi

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Abstract

Obesity is a chronic metabolic disease caused by multiple factors and also represents a systemic low-grade inflammatory state that simultaneously affects energy metabolism and immune status. Numerous studies have reported that obesity affects respiratory function to a certain extent, increases the risk of respiratory tract infections, and modulates the body' s ability to clear pathogens, leading to polarized patient outcomes. Currently, the underlying mechanism remains unclear; however, it is established that massive accumulation of adipose tissue increases inflammatory cell infiltration and elevates the expression levels of inflammatory mediators and adipokines, which may constitute the primary mechanism by which obesity alters pulmonary sensitivity to pathogenic microorganisms. This article provides a brief exposition of the potential mechanisms through which obesity influences respiratory anti-infection capabilities, thereby establishing a foundation for in-depth investigation of the relationship between obesity and respiratory tract infections.

Full Text

Mechanisms of Obesity' s Impact on Respiratory Anti-infection

WAN Taomei, GAN Linli, ZUO Zhicai*, REN Yi
(Key Laboratory of Animal Disease and Human Health of Sichuan Province, Key Laboratory of Environmental Hazard and Animal Disease of Sichuan Province, College of Veterinary Medicine, Sichuan Agricultural University, Ya' an 625014, China)

Abstract: Obesity is a chronic metabolic disease caused by multiple factors and represents a state of systemic low-grade inflammation that affects both energy metabolism and immune status. Numerous studies have reported that obesity influences respiratory system function, increasing the risk of respiratory

tract infections while modulating the body' s ability to clear pathogens, leading to divergent clinical outcomes. Although the precise mechanisms remain unclear, it is evident that the massive accumulation of adipose tissue increases inflammatory cell infiltration and elevates the expression levels of inflammatory mediators and adipokines, which may be the primary factors altering lung susceptibility to pathogenic microorganisms. This review briefly elaborates on the potential mechanisms by which obesity affects respiratory anti-infection, laying a foundation for further exploration of the relationship between obesity and respiratory infections.

Keywords: obesity; respiratory tract; infection; mechanism

The respiratory system serves as the primary site for gas exchange between the body and the external environment, making it highly vulnerable to pathogen invasion. During infection, the immune system functions to defend against pathogen proliferation and dissemination, but this capacity is influenced by various factors including nutritional status and body condition. Obesity is a chronic metabolic disease characterized by excessive fat accumulation and ectopic lipid deposition, which alters physiological conditions including immune function, thereby affecting respiratory system sensitivity to inflammatory stimuli. In 1993, Hotamisligil et al. [**?**] discovered that tumor necrosis factor-α (TNF-α) was highly expressed in adipose tissue and circulating blood of obese animal models, first establishing a link between obesity and inflammation. Subsequent investigations have shown that obesity places the lungs in a highly pro-inflammatory state, not only increasing pneumonia risk [**?**] and enhancing inflammatory responses [**?**], but also correlating positively with mortality [**?**, **?**]. However, other studies have reported that while obesity increases pneumonia incidence, it reduces mortality in pneumonia patients, suggesting an important protective role against infection [**?**, **?**]. Currently, few studies have examined how obesity affects lung susceptibility to pathogens in animal models, though Gebrehiwot et al. [**?**] analyzed the relationship between gross pulmonary lesions and age/nutritional status in 1,148 slaughtered cattle, finding that obese cattle had higher incidences of pulmonary congestion and abscesses but significantly lower rates of emphysema. Mouse experiments have demonstrated that obesity increases the severity of pulmonary infections, impairs macrophage phagocytic capacity, prolongs spontaneous recovery time, and elevates mortality [**?**, **?**], though the specific mechanisms remain unclear. This review summarizes the potential mechanisms by which obesity influences respiratory anti-infection, providing a foundation for deeper investigation into the obesity-lung infection relationship and offering new perspectives for animal-related research.

Obesity, particularly abdominal obesity, can mechanically impede diaphragmatic and airway smooth muscle movement, decreasing thoracic and lung compliance, increasing airway resistance, and limiting lung capacity, ultimately impairing ventilation function [**?**]. These physiological alterations increase lung infection susceptibility. Additionally, obesity induces extensive collagen fiber

deposition around bronchi and increases matrix metalloproteinase-9 (MMP-9) expression, promoting pulmonary fibrosis and airway remodeling that affects disease severity and treatment outcomes [**?**]. However, researchers have found that while respiratory symptoms improve during weight loss interventions in obese patients, airway hyperresponsiveness (AHR) does not significantly decrease [**?**]. Even after surgical removal of alveolar load, AHR persists in obese animals at significantly higher levels than in non-obese animals [**?**], indicating that mechanical factors are not the primary mechanism underlying obesity' s effects on respiratory inflammation.

2.1 Glucose and Lipid Metabolism Disorders

In obesity, excessive accumulation of triglycerides (TG) in adipocytes impairs lipid storage capacity, elevating circulating TG and free fatty acid (FFA) levels [**?**]. As an intracellular second messenger, TG directly activates intracellular signaling kinases such as protein kinase C (PKC), c-Jun N-terminal kinase (JNK), and inhibitor of nuclear factor kappa-B kinase (IKK) [**?**], mediating transcription and expression of specific factors. FFAs serve as natural ligands for Toll-like receptor 4 (TLR4) [**?**]; upon binding, they directly activate downstream signaling pathways including myeloid differentiation factor 88 (MyD88) and phosphatidylinositol 3-kinase (PI3K) [**?**], while also indirectly activating JNKs and IKKs through PKC activation [**?**], thereby influencing immune cell metabolism and function. Key nuclear receptors regulating lipid metabolism—peroxisome proliferator-activated receptors (PPARs) and liver X receptors (LXRs)—also participate in immune processes and inflammatory responses. In immune cells such as macrophages, T cells, B cells, and dendritic cells, PPAR expression, along with LXR expression in macrophage nuclei, is affected by nutritional status. In obesity, increased lipid ligands like FFAs and cholesterol enhance PPAR and LXR binding and activation, which inhibits IKK activity, increases inhibitor of NF- B (I B) phosphorylation, and reduces DNA binding site exposure, thereby suppressing the nuclear transcription factor kappa-B (NF- B) signaling pathway and decreasing inflammatory factor gene expression. Moreover, LXRs inhibit pathogen-induced macrophage apoptosis, exerting important anti-inflammatory effects [**?**, **?**]. However, adipose tissue metabolites such as reactive oxygen species (ROS) generated from fatty acid or glucose oxidation in mitochondria can also activate inflammatory protein kinases JNKs and IKKs, enhancing NF- B transcriptional activity, while high ROS levels induce apoptosis and trigger inflammation [**?**].

2.2 Inflammatory Cell Infiltration

Adipose tissue is a complex organ composed primarily of adipocytes, extracellular matrix, vasculature, nervous tissue, preadipocytes, fibroblasts, stem cells, and immune cells. Studies show that total white blood cell counts are significantly elevated in obese individuals, with neutrophils showing both increased numbers and enhanced activity, indicating that nutritional status affects leuko-

cyte proliferation and differentiation [?, ?, ?]. Increased blood leukocytes promote inflammatory cell infiltration in the lungs; research demonstrates that obesity elevates total leukocyte counts in bronchoalveolar lavage fluid and induces inflammatory cell aggregation around airways, bronchi, and alveolar septa, predominantly neutrophils and macrophages [?, ?]. Macrophage numbers in adipose tissue correlate with obesity indices and adipocyte size; adipose tissue lacking macrophages shows reduced TNF-α and other pro-inflammatory cytokines, indicating that macrophage infiltration is a central event regulating inflammatory responses in obesity [?, ?]. Some scholars propose that macrophages and adipocytes differentiate from common precursor cells; in obese individuals, macrophages cluster around apoptotic adipocytes, clearing senescent and dead cells while preventing excessive adipocyte expansion, thereby controlling obesity progression. Obesity severity can also shift macrophages from the anti-inflammatory M2 phenotype to the pro-inflammatory M1 phenotype, altering their function [?]. Additionally, recruitment of CD8+ T cells [?, ?], CD4+ T cells [?, ?], CD3+ T cells [?], B lymphocytes [?, ?], mast cells [?], and eosinophils [?] in adipose tissue directly mediates inflammation and promotes macrophage aggregation, differentiation, and activation. Among these, different CD4+ T cell subsets exert distinct effects in obese adipose tissue; in diet-induced obesity, visceral adipose tissue shows increased Th1 cells and decreased Th2 cells, elevating the Th1/Th2 ratio. This pro-inflammatory state cannot be reversed by increasing Th2 cells alone, as Th2 cells also promote macrophage transition from M1 to M2 phenotype [?].

2.3 Disruption of Adipocytokine Balance

The complexity of adipose tissue composition establishes it not only as an important energy storage depot but also as a large, highly active endocrine organ that secretes numerous bioactive substances. These include adipocyte-specific factors such as leptin, adiponectin, and resistin, as well as non-specific factors like TNF-α and interleukin-6 (IL-6) [?]. Collectively termed adipocytokines, these molecules influence energy metabolism in adipose and other tissues through autocrine or paracrine actions, regulate inflammatory levels and immune function, and play important roles in respiratory infection pathogenesis.

2.3.1 Non-specific Adipokines 2.3.1.1 TNF-α

TNF-α is a multifunctional cytokine primarily secreted by activated monocytes/macrophages, with adipose tissue macrophages being an important source. Studies report significantly increased TNF-α gene expression and protein levels in both circulation and adipose tissue of obese individuals [?, ?]. Analysis of obese mouse adipose tissue separating adipocytes from non-adipocytes revealed that adipocytes express TNF-α more abundantly than other cells (macrophages, mast cells, etc.), making them the primary source [?]. Two structurally distinct TNF-α receptors (TNF-R , TNF-R) are expressed on all cells except red blood cells, differing significantly in binding affinity and intracellular signaling pathways. Upon stimulation, TNF-R binds TNF receptor-associated death do-

main (TRADD), activating apoptotic and pro-inflammatory pathways through FADD protein while enhancing NF- B transcription via TRAF2 and receptor-interacting protein [**?**], promoting inflammation. Investigations of respiratory infection patients show elevated serum TNF-α levels in acute lower respiratory infections [**?**, **?**]. Animal experiments demonstrate that TNF-α enhances resistance in pneumonia mice, reduces mortality, improves blood pathogen clearance, increases neutrophil recruitment, and correlates positively with pulmonary bacterial load [**?**, **?**]. In obese mice with pneumonia, TNF-α gene expression is upregulated but remains significantly lower than lean mice in early stages while persisting at higher levels later, suggesting delayed inflammatory response that may relate to increased local inflammatory cells [**?**].

2.3.1.2 IL-6

IL-6 is a multifunctional cytokine secreted by diverse cells including immune cells, fibroblasts, endothelial cells, monocytes/macrophages, and various endocrine cells [**?**]. Mature adipocytes are also an important IL-6 source [**?**, **?**]. Numerous studies show dramatically elevated circulating IL-6 levels in obesity that correlate positively with obesity severity [**?**], with increased IL-6 expression and secretion from adipose tissue being the main contributor to elevated serum levels [**?**, **?**]. IL-6 binding to membrane-bound IL-6 receptor (mIL-6R) primarily activates signal transducer and activator of transcription 3 (STAT3) to inhibit apoptosis and promote epithelial cell proliferation, exerting anti-inflammatory effects. However, during infection, endothelial cells secrete large amounts of IL-6 and chemokines that recruit neutrophils and other inflammatory cells. During apoptosis, mIL-6R is proteolytically cleaved to form soluble IL-6 receptor (sIL-6R); IL-6 binding to sIL-6R alters chemokine profiles (converting CXC to CC types), increases monocyte/macrophage and T lymphocyte infiltration, promotes Th2 and Th17 differentiation while inhibiting Th1 and Treg differentiation, and upregulates adhesion molecule expression, demonstrating strong pro-inflammatory properties [**?**, **?**]. Since IL-6 binds sIL-6R and mIL-6R with similar affinity, and while mIL-6R is limited to hepatocytes, macrophages, neutrophils, and certain T cells, the signal transducer gp130 is expressed on nearly all cells, IL-6 function is primarily determined by its concentration. Low IL-6 levels enhance neutrophil bactericidal capacity and downregulate cytokine expression, improving infection resistance, but excessive IL-6 induces inflammatory responses [**?**, **?**]. In mouse bacterial pneumonia models, IL-6 mRNA and protein concentrations are persistently elevated in local tissues and circulation; IL-6 knockout results in faster death, higher mortality, and increased levels of pro-inflammatory cytokines (TNF-α, IL-1β, IFN-γ), anti-inflammatory factors (IL-10), and bacterial load [**?**, **?**]. Obese mice with lung injury exhibit higher IL-6 levels than normal mice, promoting neutrophil recruitment to lungs and enhancing epithelial cell damage, resulting in stronger pulmonary inflammation than lean mice [**?**]. Furthermore, chronic IL-6 overexpression in lung tissue induces monocyte/macrophage infiltration and pronounced inflammation [**?**].

2.3.2 Specific Adipokines 2.3.2.1 Leptin

In 1994, Zhang et al. [?] cloned the mouse obesity gene through positional cloning; its protein product suppresses food intake and reduces body weight, hence named leptin, which is primarily secreted by adipose tissue. Leptin activates downstream JAK-STAT-NF- B signaling pathways by binding to transmembrane functional receptors (Ob-Rb), broadly participating in immune system homeostasis and immune cell proliferation/differentiation while inhibiting apoptosis and exerting anti-inflammatory effects [?, ?]. In 1998, Lord et al. [?] first proposed that leptin induces peripheral blood lymphocyte proliferation, specifically modulates naive and memory T cell activity, promotes Th1 cytokine production, inhibits Th2 cytokine secretion, and regulates infection-induced Th1/Th2 imbalance, alleviating immunosuppression caused by acute starvation and improving immune dysfunction from nutritional deficiency. Additionally, leptin enhances erythropoietin activity and stimulates erythropoiesis [?]. In the lungs, leptin acts as a growth factor directly affecting pulmonary contractile function and indirectly influences ventilation through central respiratory regulators [?]. During bacterial pneumonia in obese individuals, leptin plays important anti-inflammatory roles by enhancing macrophage phagocytic capacity, accelerating pathogen clearance, and reducing infection mortality while controlling expression levels of inflammatory cytokines like TNF-α to decrease pneumonia severity and inhibit inflammation progression [?, ?].

2.3.2.2 Adiponectin

Adiponectin is a hormone-like protein specifically secreted by adipocytes discovered by four different research groups using different methods in 1995 and 1996 [?, ?, ?, ?], exerting diverse physiological functions across tissues. In the liver, adiponectin reduces fatty acid utilization and promotes FFA oxidation, indirectly affecting inflammation. In vascular walls, it decreases adhesion factor expression, inhibits monocyte adhesion, and interferes with TNF-α signaling by suppressing scavenger receptor expression and TNF-α synthesis in macrophages, reducing foam cell levels and directly participating in immune regulation. In vivo, adiponectin binding to specific receptors directly activates PPAR-α, AMP-activated protein kinase (AMPK), mitogen-activated protein kinases (MAPK), and NF- B signaling pathways, influencing cell differentiation and secretory function [?, ?]. In mouse models of bronchial asthma, adiponectin gene expression and protein secretion are significantly elevated, and exogenous adiponectin markedly attenuates allergen-induced airway hyperresponsiveness and allergic inflammation in both healthy and adiponectin-knockout mice [?, ?], demonstrating clear anti-inflammatory effects in respiratory diseases.

2.3.2.3 Resistin

Resistin is a small protein specifically secreted by adipose tissue discovered in 2001 and named for its potent insulin resistance effects. Subsequent studies revealed high resistin expression in bone marrow cells [?] and homology with found-in-inflammatory-zone 1 (FIZZ1) [?], also known as FIZZ3, indicating resistin' s involvement in inflammation. Resistin primarily interacts with cell surface TLR4 to activate MAPK and NF- B signaling pathways, mediating cytokine ex-

pression, though whether this interaction is direct and specific remains unclear [?, ?]. Lee et al. [?] found that resistin directly binds to CAP1 on monocyte surfaces, activating PKA and NF- B pathways to upregulate pro-inflammatory cytokine gene expression and enhance monocyte chemotaxis and migration. Resistin reduces polymorphonuclear leukocyte (PMNL) oxidative burst induced by *E. coli* through PI3K signaling, modulating PMNL and CD4+ T lymphocyte chemotaxis in a reversible, concentration-dependent manner—promoting migration at certain concentrations but inhibiting it at excessive levels [?]. However, resistin absolutely positively correlates with adhesion molecule induction [?, ?] and amplifies this effect by enhancing suppressor of cytokine signaling-3 (SOCS-3) secretion in endothelial cells [?], promoting monocyte-endothelial adhesion [?]. Additionally, resistin induces Treg cell expansion by activating dendritic cells (DCs) [?] while reducing DC antigen presentation and bacterial phagocytosis [?], demonstrating clear pro-inflammatory properties.

Obesity represents a chronic, systemic low-grade inflammation that moderately upregulates circulating white blood cell counts and inflammatory mediators including cytokines, chemokines, and adhesion factors. This controlled inflammation is important for maintaining physiological balance and health. However, when obese individuals encounter pathogen invasion or external stimuli, excessive and uncontrolled inflammation disrupts homeostasis, causing irreparable damage. Obesity affects not only mechanical lung function but also transports locally increased inflammatory mediators to the lungs via systemic circulation, influencing pulmonary physiology and pathogen susceptibility. However, most current research models investigating obesity-infection relationships focus on gene knockout mice, which do not reflect natural obesity physiology in humans and animals, and few reports address obesity and respiratory infections in animals. Diet-induced obesity (DIO) models more closely approximate natural obesity and should be utilized more extensively in future research, with systematic statistical analysis of animal nutritional status and disease conditions to provide more direct evidence for obesity' s impact on respiratory infections in animals.

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Note: Figure translations are in progress. See original paper for figures.