Review Article

Neutrophil gelatinase-associated lipocalin as a potential therapeutic integrator of glycolipid metabolic and inflammatory signaling

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ABSTRACT

Metabolic syndrome constitutes a group of metabolic conditions that increase the risk of developing diseases, including cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), obesity and type 2 diabetes mellitus (T2DM) etc. Subclinical inflammation is a candidate etiological factor in the pathogenesis of metabolic syndrome and in the progression of related diseases. Although studies have revealed that subclinical inflammation was activated by intermediary products of basic metabolic processes, the cellular and molecular mechanisms in this association remain largely uncharacterized. Recently, increasing evidence suggests that neutrophil gelatinase-associated lipocalin (NGAL) not only plays a significant role in the glycolipid metabolism, but also modulates immune and inflammatory responses in macrophages. Taking together the ability of NGAL in metabolic and inflammatory signaling, these data suggest that NGAL may be a potential therapeutic target for metabolic and inflammatory signaling for intervention in human glycolipid metabolic disease. This review focuses on current knowledge of the integrators role of NGAL in both glucose and lipid metabolism and inflammatory signaling and discusses the potential therapeutic target in the treatment of glycolipid metabolic-related disease.

Keywords: Glycolipid metabolic dysfunction, Inflammation, Metabolic disease, Neutrophil gelatinase-associated lipocalin

INTRODUCTION

Metabolic disease can be triggered by chronic excess of lipids and glucose. On the other hand, inflammation can trigger insulin resistance or metabolic dysfunction under defined conditions.¹ It is possible to enter the network from an inflammatory or metabolic gateway and still end up with the same vicious loop. In the past decade, much effort has been made to understand the mechanisms how lipids and glucose are handled by macrophages and how inflammation could promote the glycolipid metabolic related disease process.² Here, we also provide an overview of these two fields. Metabolic dysfunction triggered inflammation, in turn low-grade chronic inflammation aggravates metabolic dysfunction, and end up with the vicious loop.³ Glycolipid metabolism and inflammation are highly integrated and the proper function of each is dependent on the other, which are the most essential requirements for survival.⁴ So, choose way of proper regulate and control of low-grade chronic inflammation in metabolic dysfunction is very important and useful under present conditions.

This review examines the current knowledge about the physiological function of NGAL in glycolipid metabolism and inflammation, which highlights the current understanding of the possible mechanisms underlying the association between glycolipid...
metabolism and low-grade chronic inflammation. Finally, the utility of NGAL as potential therapeutic agent in glycolipid metabolic-related disease is also discussed.

**Neutrophil gelatinase-associated lipocalin (NGAL)**

NGAL also known as 24p3, lipocalin 2 (LCN2), is a 25-kDa secretory glycoprotein that belongs to the lipocalin superfamily, which was initially purified from neutrophil granules. Homologous proteins have been identified in mouse (24p3/uterocalin) and rat (alpha 2-microglobulin-related protein/neu-related lipocalin). Like the other members of the lipocalin superfamily, structural data have confirmed that it shares a barrel shaped tertiary structure with an eight-stranded beta-barrel, which can bind to and transport small lipophilic substances and other hydrophobic molecules, such as prostaglandins, retinoids, hormones and fatty acids. NGAL is expressed in several tissues including neutrophils, liver, lung, kidney, adipocytes, astrocytosis and macrophages. It has various functions such as the transport of fatty acids and iron, the induction of apoptosis, and roles in innate immunity and inflammation. NGAL protects against bacterial infection and stress and is an acute phase protein induced in response to injury, infection, or other inflammatory stimuli. NGAL is also an inflammatory risk factor for stroke, bowel disease and chronic heart disease since its levels in both urine and plasma rise under these conditions, however the biological roles of elevated NGAL are not yet clear. NGAL concentrations were also directly correlated with adiposity, hypertriglyceridemia, hyperglycemia and insulin resistance in patients with obesity-related metabolic and cardiovascular diseases.

**Inflammation in metabolic disease**

The traditional features of inflammation are described as the principal response of the body invoked to deal with the physical, chemical, or biological harmful injuries, which hallmarks of which include swelling, redness, pain and fever. If successful, the injurious agent is eliminated and inflammation resolution and tissue repair follow. If the response is not properly phased, however, the process can develop into a chronic low-grade inflammatory state that may trigger different diseases under pathological conditions. Metabolic disorders including obesity, type 2 diabetes mellitus, nonalcoholic fatty liver disease, Alzheimer’s disease and atherosclerosis. It is now widely appreciated that inflammation plays a key role in the initiation, propagation, and development of metabolic diseases. The inflammatory state that accompanies the metabolic syndrome shows a quite peculiar presentation, without infection or sign of autoimmunity or massive tissue injury. It is often called “low-grade” chronic inflammation or “subclinical” inflammation, as a term to define an intermediate state between basal and inflammatory states, which was characterized by abnormal cytokine production, increased acute-phase reactants and other mediators, and activation of a network of inflammatory signalling pathways. Researchers have attempted to name this inflammatory state as “metaflammation”, meaning metabolically triggered inflammation. Further studies find that metabolic diseases such as obesity are characterized by a subclinical inflammatory state that contributes to the development of insulin resistance and atherosclerosis. Inflammatory condition that is associated with metabolic disorders plays an important part in the aetiology of the metabolic diseases and largely contributes to the related pathological outcomes.

Studies have shown that chronic low-grade inflammation is a common feature in the metabolic diseases such as atherosclerosis, diabetes, insulin resistance. However the inflammatory process that characterizes the metabolic diseases seems to have its own unique features, its mechanisms being far from fully understood. Although the cause and the molecular participants in this process remain incompletely defined, recent data have revealed that elevated levels of the inflammatory marker have been associated with components of the metabolic disorders. The plasma concentration of inflammatory mediators is increased in the insulin-resistant states of obesity and type 2 diabetes. These markers of inflammation include acute phase proteins, pro-inflammatory cytokines, JNK family of kinases, adhesion molecules and adipokines (proteins secreted by adipose tissue) such as tumor necrosis factor α (TNF-α), IL-6, high-sensitivity C-reactive protein (hs-CRP), fibrinogen, and plasminogen activator inhibitor-1 (PAI-1). Previous researches have shown that MHV68 infection promoted fatty liver, hypertriglyceridemia, insulin resistance, and hyperinsulinemia in association with elevated inflammatory cytokines. Inflammation also induced insulin resistance and increased serum free fatty acid levels in C57BL/6J mice. In the livers of MHV68-infected C57BL/6J mice, SREBP1, FAS, ACC levels were increased. The inflammatory stress upregulated mRNA and protein expression of sterol regulatory element binding protein 1, fatty acid synthase, and acetyl CoA carboxylase alpha, while inhibited these molecules expression in adipose. Thus, inflammation disturbed free fatty acid homeostasis and caused insulin resistance. So chronic systemic inflammation increased lipogenesis in non-adipose tissues and lipolysis in white adipose tissue, resulting in ectopic lipid deposition in non-adipose tissues.

Although the markers of chronic inflammation are clearly established, the factors responsible for the initiation and maintenance of the chronic inflammation remain to be elucidated. Lipids can undergo oxidative modification by lipoxygenases, cyclooxygenases, myeloperoxidase, and other enzymes. Oxidized phospholipids can induce inflammatory molecules in the liver and other organs. Macrophages accumulate lipids from ox-LDL leading to lipid-loaded foam cell formation, which lead to a sustained chronic inflammation. Therefore, metabolic dysfunction triggered inflammation, in turn chronic
inflammation aggravated metabolic dysfunction, and their action mechanism needs further research.

**Neutrophil gelatinase-associated lipocalin in metabolism**

NGAL as a cytokine playing a critical role in the regulation of body fat mass, energy metabolism, glucose and lipid metabolism, and insulin resistance. In humans, circulating NGAL concentrations were positively correlated with adiposity, hypertriglyceridemia, hyperglycemia, and the insulin resistance index, while changes were normalized after rosiglitazone treatment. NGAL mRNA expression in adipose tissue and liver and its circulating concentrations were significantly increased in diabetic or obese mice. Expression of NGAL is elevated by agents that promote insulin resistance and is reduced by Thiazolidinediones, and exogenous NGAL promotes insulin resistance in cultured hepatocytes. Clinical researches also discovered that serum NGAL might be useful for evaluating the outcomes of various clinical interventions for obesity-related metabolic and cardiovascular diseases. Some research has found that serum NGAL was significantly higher in subjects with isolated impaired fasting glucose, isolated impaired glucose tolerance, combined impaired fasting glucose/impaired glucose tolerance and newly-diagnosed type 2 diabetes than in those with normal glucose regulation. Findings suggest that NGAL elevation was clearly associated with a higher risk for impaired glucose regulation. Elevated serum NGAL is closely and independently associated with impaired glucose regulation and type 2 diabetes. However, on the other hand its disruption in mice resulted in significantly potentiated diet-induced obesity, dyslipidemia, fatty liver disease, and insulin resistance. NGAL-/ mice have increased hepatic gluconeogenesis, decreased mitochondrial oxidative capacity, impaired lipid metabolism, and increased inflammatory state under the high fiber diet condition. As a result, in the absence of NGAL, mice developed insulin resistance, dyslipidemia, and fatty liver disease. However, the mechanisms underlying this phenomenon have largely remained elusive.

In the past decade, enormous researches have identified NGAL as a central player in glucose and lipid metabolism. It has been implicated in almost all aspects of glycolipid metabolic disorders, including obesity, insulin resistance, dyslipidemia. Evidence for NGAL in regulating glucose and lipid metabolism is not only provided by in vivo studies but also in vitro studies. Known as ligand-regulated transcription factors, NGAL plays central regulatory roles in lipid uptake, metabolism and efflux. The experimental results demonstrate that in the absence of NGAL, mice showed decreased adipose PPARγ expression. It has been clearly demonstrated that lipogenesis and insulin sensitivity are differentially regulated by PPARγ activation; at the same time PPARγ activation requires ligands and coactivator binding. NGAL is an important regulator for the activation of PPARγ that controls adipogenesis and lipogenesis in adipose tissue and liver. In this way, NGAL is a critical role in the regulation of glycolipid metabolism and energy metabolism. The mechanism of NGAL in glycolipid metabolism perhaps includes other levers. Finally, the physiological significance of change of NGAL in glucose and lipid metabolism is complex and obviously required further investigation. Taken together, the results show that NGAL functions as an important cytokine of lipocalin superfamily, contributes greatly to energy homeostasis, and participates in glucose and lipid metabolism.

**Neutrophil gelatinase-associated lipocalin in inflammation**

NGAL is not only important in the regulation energy metabolism, glucose and lipid metabolism, but also in regulating inflammation which is important in diabetes and metabolic syndrome. Clinical findings in humans and experimental studies in animal models demonstrate that NGAL play a key role in acute infection and chronic inflammation. NGAL is an inflammatory marker closely related to “low-grade” chronic inflammation. In humans, there was also a strong positive association between NGAL concentrations and high sensitivity C-reactive protein (hs-CRP), independent of age and sex.

Several inflammatory stimuli, such as lipopolysaccharides, IL-1β, IL-9, IL-10 can markedly induce NGAL expression and secretion in macrophages and adipocytes. NGAL is strongly induced by the pro-inflammatory cytokine interleukin-1β via nuclear factor-kB activation, but not by the profibrotic cytokines platelet-derived growth factor and transforming growth factor-β. The proinflammatory transcription factor NF-kB has been shown to trans activate NGAL expression through binding with a consensus motif in the promoter region of the NGAL gene. In response to IL-1β stimulation, Increases in NGAL expression in human and rat vascular smooth muscle cells, were attributed to activation of the NF-kB signaling pathway.

NGAL induction is governed solely by NF-kB and its co-factor IκB-zeta. The gene encoding NGAL is strongly up-regulated by IL-1β in an NF-kB-dependent manner but not by tumor necrosis factor (TNF)-alpha, another potent activator of NF-kB. However, NGAL is strongly induced by stimulation with TNF-α in the presence of IL-17. Co-stimulation with IL-17 leads to accumulation of IκB-zeta mRNA and IκB-zeta protein, which can bind to NF-kB on the NGAL promoter and thus induce it expression. Further study shows that the expression of NGAL correlate to liver damage and resulting inflammatory responses, rather than to the degree of liver fibrosis, which in fact may imply a distinct diagnostic value as an early biomarker of liver inflammation. On the other hand, NGAL is the major acute-phase protein whose gene expression is mainly controlled by IL-6. The bacterial
clearance effect was partly due to their upregulation of the antibacterial protein NGAL in acute-phase reaction. When treated rat hepatocytes with IL-9, induced a considerable time dependent upregulation of NGAL.\textsuperscript{38,39} In mycobacterial pulmonary infections, NGAL promotes neutrophil recruitment and constrains T cell lymphocytic accumulation and inflammation by inhibiting inflammatory chemokines.\textsuperscript{40,41} These studies suggest that the acute phase response to acute endotoxemia involves induction of NGAL. Altogether, NGAL is strongly increased in experimental models of acute and chronic injuries. This protein may be important in restoring tissue homeostasis following LPS-induced injury and chronic inflammation.

In other studies, NGAL activated the anti-inflammatory nuclear receptor peroxisome proliferator-activated receptor (PPAR)\textsubscript{γ} that is involved in anti-inflammatory macrophage activation.\textsuperscript{43} NGAL upregulates inflammatory gene expression including MCP-1, IP-10, and VCAM-1 in vitro and in vivo.\textsuperscript{42} Both suppression of inflammation and renal regeneration might require S1P receptor 3 (S1P3) signaling and downstream release of neutrophil gelatinase-associated lipocalin (NGAL/Lcn-2) from macrophages. macrophage-dependent S1P-S1P3-Lcn-2 axis that might be beneficial for suppression of inflammation of kidney after an ischemic insult.\textsuperscript{43}

Although NGAL is expressed in many aseptic inflammatory conditions, its role in these conditions remains unclear. Recent research suggests that NGAL expression at the protein level is rapidly increased 12-fold at 1 d after spinal cord contusion injury and decreases gradually thereafter, being three times as high as control levels at 21 d after injury. NGAL expression is strongly induced after contusion injury in astrocytes, neurons, and neutrophils. This change was accompanied by a reduction in the expression of several pro-inflammatory chemokines and cytokines.\textsuperscript{34,45}

NGAL was found to be significantly decreased in CSF of human patients with mild cognitive impairment and Alzheimer's disease and increased in brain regions associated with Alzheimer's disease pathology in human postmortem brain tissue, NGAL maybe as a molecular actor in neuroinflammation in early clinical stages of Alzheimer's disease.\textsuperscript{46} Application of NGAL-blocking antibodies before airway challenges resulted in increased inflammation. These data indicate a protective role for NGAL in “low-grade” chronic inflammation. NGAL, as a novel autocrine and paracrine adipokine, acts as an antagonist to the effect of inflammatory molecules on inflammation and secretion of adipokines.\textsuperscript{47,48}

Conclusion and perspective

In summary, metabolism and inflammation is the complex biological systems. We suggest that inflammation play a role in the pathogenesis of metabolic related disease. Therefore, controlling this inflammation could be a promising strategy in the treatment of patients. There is still much to be studied regarding NGAL as crucial point between low-grade chronic inflammation and metabolic dysfunction. However, animal and cross-sectional human studies may be having revealing conflicting results. The commonly used animal model does not always fully mimic human diseases in certain situations. Future work will continue to define and explore the role NGAL execute control of metabolism and inflammation and integrate these pathways in complex biological systems and will further explore the NGAL signaling pathway as a target of inflammation in human metabolic dysfunction.

Studies over the last 10 years have shown an association between markers of inflammation and metabolic dysfunction.

**Different research proved following facts**

- Chronic low-grade inflammation is a common feature in the metabolic diseases such as atherosclerosis, diabetes and NAFLD, and inflammation plays a key role in the initiation, propagation, and development of metabolic diseases.
- NGAL is an inflammatory marker closely related to “low-grade” chronic inflammation. The NGAL level was one of the useful indicators of early stage in inflammation.
- NGAL was a critical role in the regulation of body energy metabolism, glucose and lipid metabolism, insulin resistance, which were the basis of metabolic disease.

Orders of evidence indicate that the NGAL levels positively correlate with glycolipid metabolism, energy regulation and low-grade chronic inflammation, which are all associated with metabolic diseases such as atherosclerosis, diabetes, and NAFLD.

According to the evidence we hypothesize that NGAL may be a crucial link point between low-grade chronic inflammation and glycolipid metabolism disorders. We predict that a better understanding of NGAL crosstalk between glucose and lipid metabolism and low-grade chronic inflammation may ultimately lead to the development of etiological, mechanical information for early stage of metabolic diseases in which glycolipid metabolism and inflammation also play important roles.

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