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THE ROLE OF LIPOCALIN-2 IN OBESITY AND ENERGY METABOLISM.

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Abstract:

Lipocalin-2 (LCN2), also known as neutrophil gelatinase-associated lipocalin (NGAL), is a protein that plays a role in inflammation, immunity, and various physiological processes. It is part of the lipocalin family, which includes proteins that bind small hydrophobic molecules like lipids and steroids.NGAL is involved in innate immunity by sequestering iron and preventing its use by bacteria, thus limiting their growth. It is expressed in neutrophils and in low levels in the kidney, prostate, and epithelia of the respiratory and alimentary tracts. NGAL is used as a biomarker of kidney injury LCN2 is widely expressed across various tissues, including immune cells, bone, adipose tissue, liver, kidneys, lung, spleen, and epithelial cells, and exhibits sex- and fat depot-specific expression patterns. Structurally, LCN2 contains a hydrophobic lipidbinding pocket and glycosylation sites, enabling it to interact with diverse ligands and form dimers. In innate immunity, LCN2 plays a critical role by sequestering iron-laden siderophores, thereby restricting bacterial growth. Beyond its role in infection control, LCN2 is implicated in metabolic inflammation and diseases such as obesity and diabetes. Recent research has highlighted a pivotal role for LCN2 in mitochondrial phospholipid metabolism and mitochondrial function. In metabolic diseases and mitochondrial metabolism, LCN2 appears to display paradoxical effects. While some studies link it to improved insulin sensitivity, glucose regulation, and mitochondrial function, others associate it with insulin resistance, obesity, and mitochondrial dysfunction. These inconsistencies may arise from differences in experimental conditions and study populations.

Keywords: Lipocalin 2; obesity; metabolic inflammation; paradaxial effects; β-Barrel Proteins; siderophores;

1. INTRODUCTION

Lipocalin 2 (LCN2), also known as neutrophil gelatinase-associated lipocalin, is a 25 kD secreted protein first characterized in neutrophils [1,2]. This 178-amino acid protein has several notable structural features, including a hydrophobic binding pocket for lipid interactions, glycosylation at asparagine residue 65, and an unpaired cysteine at residue 87, which facilitates dimerization with other proteins [2,3]. LCN2 is widely expressed in various tissues, including immune cells, adipose tissue, liver, kidneys, bone marrow, prostate, and epithelial tissues exposed to microorganisms, such as the trachea, lungs, stomach, salivary glands, colon, and uterus [4–5]. This broad tissue distribution underscores its roles in immune defense, inflammation, and metabolic regulation. LCN2 has also been implicated in metabolic processes, particularly obesity and diabetes, where its levels are often upregulated. However, its effects on metabolism appear paradoxical. While some studies indicate LCN2 enhances insulin sensitivity and benefits glucose regulation, others associate it with glucose intolerance, insulin resistance, and obesity [6]. These discrepancies may stem from variations in experimental conditions or differences in population characteristics across human studies. Overall, LCN2 plays diverse roles in inflammation, iron metabolism, and metabolic regulation, exerting both protective and detrimental effects depending on the context. Further research is essential to unravel its complex functions in metabolic disorders. This review offers an up-to-date overview of LCN2's multifaceted role in obesity, diabetes, energy balance, and mitochondrial metabolism. Additionally, it aims to provide a clearer interpretation and understanding of LCN2's paradoxical effects, as characterized by various research groups under differing conditions. Lipocalins

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are a diverse family of proteins that participate in various biological processes. RBP4, one of the lipocalin subfamily members, has been identified as an adipokine that affects glucose metabolism and insulin sensitivity [7]. RBP4 expression in adipose tissue, as well as circulating RBP4, were increased in several models of rodent obesity [7]. Overexpression or loss of function analysis in mice suggests that RBP4 functions as an antagonist of insulin action [7]. The circulating levels of RBP4 were elevated in individuals with obesity, showing a negative correlation with insulin sensitivity [8] and a positive correlation with the percent abdominal fat [9]. Similarly, as discussed in this review, LCN2 plays a critical role in glucose and lipid metabolism, as well as metabolic diseases.

2. LIPOCALIN 2 IN METABOLIC DISEASES

Obesity and Diabetes The role of LCN2 as an adipokine in metabolic regulation has gained significant attention in recent years. Numerous studies have explored its involvement in adipose tissue remodeling and metabolic regulation, particularly in the context of obesity and diabetes.

2.1. Circulating Lipocalin 2 Levels Correlate with Obesity and Diabetes

As discussed earlier, adipose Lcn2 expression is upregulated in both genetically modified and diet-induced obese mouse models. Studies in mice have demonstrated increased circulating LCN2 levels in obesity. For instance, in HFD-induced obesity, serum LCN2 levels increased by 25% after 16 weeks of HFD feeding in normal mice. Furthermore, an approximately twofold increase in serum LCN2 levels was seen in obese insulin-resistant female leptin-deficient ($Lep^{ob/ob}$) mice and male leptin receptor-deficient ($Lepr^{db/db}$) mice compared to wild-type (WT) mice. Similarly, in a human study, women with severe obesity showed significantly elevated circulating LCN2 levels compared to individuals with normal weight [10]. Mosialou et al. explored the systemic role of LCN2 as a secreted protein in glucose metabolism in the context of prediabetes and type 2 diabetes mellitus (T2DM) [11]. Their study involved two cohorts of post-menopausal women (n = 88 and n = 54) and one male cohort (n = 24). Over five years, they found no correlation between fasting plasma glucose and serum LCN2 levels in post-menopausal women. However, serum LCN2 levels showed a strong positive correlation with body mass index (BMI), waist circumference, serum insulin levels, homeostatic model assessment of insulin resistance (HOMA-IR), and β-cell function (using HOMA-β). This correlation intensified with increasing obesity. Serum adiponectin, on the other hand, was inversely correlated with serum LCN2 levels. Logistic regression revealed that increased HOMA-IR was strongly associated with the highest quartile of LCN2 levels. However, baseline LCN2 levels were not predictive of T2DM onset after five years, while HOMA-IR significantly correlated with new T2DM cases [11]. In a separate cohort of 54 postmenopausal women with T2DM, as the disease progressed, the relationship between serum LCN2 levels and insulin as well as hemoglobin A1c (HbA1c) reversed. A negative correlation emerged between LCN2 levels and these factors across different BMI groups [11]. This suggests that while elevated circulating LCN2 indicates metabolic dysregulation during prediabetes, in the context of T2DM, it may reflect better metabolic regulation. The authors proposed that rising LCN2 levels during the onset of insulin resistance (IR) could signify a compensatory mechanism aimed at improving β-cell function and mitigating hyperglycemia.

3. MOLECULAR MECHANISMS OF LIPOCALIN-2

Lipocalin-2 is part of the **lipocalin family** of proteins, which are primarily known for their ability to bind and transport small hydrophobic molecules, such as lipids, steroids, and vitamins. LCN2 is unique in its ability to bind **siderophores**, which are molecules secreted by bacteria to scavenge iron from their environment. Here's how LCN2 functions at the molecular level:

Binding to Siderophores and Iron Regulation:

LCN2 binds siderophores that bacteria use to capture iron. Once bound, LCN2 forms a complex with the siderophore, which prevents bacteria from acquiring iron. Since iron is crucial for bacterial growth, this serves as an antimicrobial mechanism. By sequestering siderophores, LCN2 limits the growth of pathogens and helps control bacterial infections.

Antimicrobial Activity:

In addition to limiting bacterial iron uptake, LCN2 also has direct antimicrobial properties. It can inhibit the growth of various pathogens, including **Escherichia coli (E. coli)**, **Staphylococcus aureus**, and others, contributing to its role in innate immunity.

Regulation of Inflammation:

LCN2 is upregulated during inflammatory responses, particularly in immune cells like neutrophils and macrophages. It acts as a **pro-inflammatory cytokine**, amplifying the immune response and helping to recruit immune cells to sites of infection or tissue injury. In chronic inflammation, however, it can contribute to disease progression by promoting excessive tissue damage and fibrosis.

Cellular Signaling:

LCN2 has been shown to interact with several receptors, including **receptor for advanced**

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glycation end-products (RAGE), which is involved in inflammation and tissue remodeling. Through these interactions, LCN2 can modulate signaling pathways that affect cell survival, apoptosis (cell death), and immune cell recruitment.

4. LCN2 AND INFLAMMATION

LCN2 plays a central role in **acute and chronic inflammation**. During infection or injury, the body activates a cascade of immune responses, and LCN2 is often among the first molecules produced. Here's how LCN2 influences inflammation:

Acute Inflammatory Response:

When an infection occurs, LCN2 is rapidly upregulated in various tissues, including neutrophils and epithelial cells. Neutrophils, the body's first line of defense against bacterial infection, secrete large amounts of LCN2 in response to signals such as cytokines. This boosts the immune response by recruiting more immune cells to the site of infection.

Chronic Inflammation:

In conditions like **obesity**, **diabetes**, and **cardiovascular diseases**, LCN2 is found to be persistently elevated. Chronic low-grade inflammation in adipose tissue (fat cells) leads to a cycle of continuous LCN2 production, which may contribute to insulin resistance, a hallmark of type 2 diabetes. Elevated LCN2 levels in obesity can also contribute to **atherosclerosis** and cardiovascular disease by promoting inflammatory processes that damage blood vessels.

Kidney Injury and Disease:

LCN2 is commonly used as a marker for **acute kidney injury (AKI)**. In the event of kidney damage, LCN2 is rapidly elevated in the urine and bloodstream, correlating with the degree of injury. The protein may contribute to kidney damage by amplifying inflammation and fibrosis (scarring of tissues). In chronic kidney diseases, LCN2 levels remain elevated and are used as an indicator of disease progression.

5. LCN2 IN DISEASE: CLINICAL RELEVANCE

Adipose Tissue and Inflammation

- Obesity is associated with low-grade chronic inflammation, particularly in adipose tissue.

LCN2 has been found to be upregulated in the adipose tissue of obese individuals and animal models.

- It is thought that LCN2 may act as a mediator of inflammation in adipose tissue, where it could contribute to the inflammatory environment that characterizes obesity. This inflammation can impair insulin sensitivity, which is a common issue in obesity.

LCN2 and Insulin Resistance

- Insulin resistance is a hallmark of obesity and is closely linked with metabolic diseases like type 2 diabetes.
- Elevated LCN2 levels have been observed in individuals with insulin resistance, suggesting that LCN2 may play a role in the development of this condition.
- Research shows that LCN2 can affect signaling pathways related to insulin action, possibly by interacting with certain pro-inflammatory molecules that disrupt normal insulin function.

LCN2 in Fat Metabolism

- LCN2 might also be involved in fat metabolism. Studies indicate that LCN2 regulates lipid metabolism, and its expression can influence the storage and breakdown of fat in adipose tissue.
- Some studies have shown that LCN2 can modulate the differentiation of adipocytes (fat cells), which may have implications for how the body stores fat and responds to energy demands.

Potential Biomarker for Obesity-Related Diseases

- Due to its elevated levels in obesity and its association with metabolic dysfunction, LCN2 has been proposed as a potential biomarker for obesity-related diseases, such as cardiovascular diseases and diabetes.
- Its levels can provide insight into the severity of inflammation or metabolic disturbances in obese individuals.

Therapeutic Target

- Given its central role in inflammation and metabolism, targeting LCN2 could offer potential therapeutic strategies for managing obesity and its associated complications.
- However, more research is needed to fully understand the mechanisms by which LCN2 affects obesity and whether modulating its activity can have beneficial effects on weight management or insulin sensitivity.

Diet and LCN2 Expression

- Dietary factors, such as high-fat diets, can influence the expression of LCN2. Some studies suggest that a high-fat diet may increase LCN2 levels, linking it to diet-induced obesity.
- However, certain dietary interventions, such as calorie restriction or consumption of anti-inflammatory foods, may reduce LCN2 levels and improve metabolic health.

Cardiovascular Disease:

LCN2 is involved in the inflammatory processes that lead to **atherosclerosis** (plaque build-up in arteries). In people with cardiovascular disease, LCN2 levels are often elevated in both blood and plaque tissues. It contributes to the chronic inflammatory environment within blood vessels, potentially accelerating plaque

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instability and increasing the risk of heart attacks and strokes.

Cancer:

There is emerging evidence that LCN2 plays a role in cancer biology, particularly in **tumor progression** and **metastasis**. Elevated LCN2 levels have been observed in several types of cancer, including **lung cancer**, **colorectal cancer**, and **breast cancer**. It may aid tumor cells in evading immune surveillance by modulating immune responses and promoting angiogenesis (the formation of new blood vessels to support tumor growth). Some studies also suggest that LCN2 could be used as a biomarker for detecting certain types of cancer.

5. CONCLUSIONS

LCN2 shows a sex-dimorphic and depot-dependent expression in adipose tissue, adding complexity to its role and highlighting differences between males and females. While Lcn2 has low baseline expression, its levels markedly increase in response to stress stimuli such as infection, injury, inflammation, and metabolic stress, suggesting its primary function is stress-related. LCN2 plays a significant role in energy balance, including food intake and energy metabolism in obesity and diabetes. The results from the majority of studies using Lcn2 global and tissue-specific KO models in male mice support the beneficial role of LCN2 in preventing obesity, glucose intolerance, and insulin resistance. Additionally, data from all three Lcn2 overexpression models in male mice highlight the metabolic benefits of LCN2 overexpression or increased circulating LCN2 levels. In terms of energy metabolism, LCN2 administration in male WT, *Lepr*$^{db/db}$, and Lcn2 global/osteoblast-specific KO mice has been shown to suppress food intake. Conversely, Lcn2 KO can reduce food intake suppression and weight loss during cancer-induced cachexia. Data from Lcn2 global KO and overexpression mouse models, as well as LCN2 treatment in adipocytes, provide strong evidence for LCN2's role in promoting brown adipose tissue (BAT) and beige thermogenesis, enhancing mitochondrial metabolism, and increasing energy expenditure in male mice. However, in female mice, findings are more variable and depend on the experimental model and design. In diet-induced obesity models, LCN2 appears to play a detrimental role in obesity and insulin resistance. However, in age-related obesity models, LCN2 seems to prevent visceral fat accumulation with aging. This suggests that LCN2 may have a complex role in obesity and insulin resistance in females, influenced by factors such as age and menopausal status. Further research is needed to better understand the interplay between estrogen levels and LCN2 function, particularly how estrogen may modulate LCN2 activity or vice versa in females. The effects of LCN2 on mitochondrial function appear to be double-edged. Under normal conditions, such as after a meal, LCN2 promotes mitochondrial metabolism to maintain energy balance. However, in obesity, this adaptive response is absent, leading to reduced mitochondrial metabolism and energy expenditure. In Lcn2-deficient conditions, the inability to upregulate mitochondrial oxidation under metabolic stress further impairs mitochondrial function. Conversely, the overexpression of Lcn2 in experimental models or pathological conditions (e.g., sepsis) can lead to excessive mitochondrial activation beyond cellular needs, resulting in overproduction of ROS, oxidative stress, and mitochondrial dysfunction. The detrimental effect of Lcn2 overexpression appears to be context-, sex-, and cell-type dependent. For example, thermogenic adipocytes (brown and beige adipocytes) mitigate these detrimental effects via their uncoupling system, whereas cells lacking this system, such as cardiomyocytes and renal cells, are more susceptible to damage. However, further research is needed to elucidate the complex and context-dependent functions of LCN2 and resolve conflicting findings, particularly in mitochondrial metabolism and metabolic disorders.

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