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The progress of LCN2 in the kidney and central nervous system

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Abstract: Lcn2 is a gene that encodes ferrites and has multiple physiological functions in the human body. Lcn2 can alleviate inflammation by inhibiting the production of inflammatory mediators. This makes Lcn2 a potential drug target for treating inflammatory diseases. It also participates in the progression of tumors. Lcn2 inhibits tumor growth by inhibiting tumor cell growth and migration. Lcn2 is also involved in the interaction between tumors and the immune system and may affect immunotherapy. In the process of metabolic regulation, Lcn2 can regulate the differentiation and metabolism of adipocytes, affecting obesity and metabolic diseases. Lcn2 is involved in the regulation of iron metabolism and liver inflammation. Lcn2 plays an important role in the nervous system. It may affect the development and survival of neurons and the development of neurodegenerative diseases. This article reviews the functions, mechanisms of action, biological significance, and potential clinical applications of Lcn2 under different physiological and pathological conditions. Provide researchers and clinicians with a comprehensive and accurate overview to better understand Lcn2, its function, and physiology, and its potential applications in pathological processes, thereby promoting research and clinical applications in this field.

Keywords: Neutrophil gelatinase-associated lipocalin (NGAL); Chronic inflammation; Neuroinflammation; Lipocalin 2

Introduction

Lcn2 is a natural immune protein associated with acute and chronic inflammation and related to the inflammatory status associated with the current obesity epidemic. In intestinal sepsis, Lcn2 maintains the dynamic balance of the microbiota, executes antioxidant strategies, reduces macrophage inactivation damage to the intestinal barrier, and terminates systemic inflammatory response by inducing immune cell apoptosis. Although Lcn2 exhibits anti-inflammatory activity in the intestine, it also promotes inflammatory activity in other experimental environments. In animal models of metabolic inflammation, type 2 diabetes (T2D), or nonalcoholic steatohepatitis (NASH), the increased expression of Lcn2 promotes inflammation. Lcn2 is also considered a chemokine inducer that promotes inflammation and an automatic secretion activator of astrocytes. Lcn2 derived from astrocytes acts as an inflammatory mediator in the central nervous system and plays a role in neuroinflammatory diseases. The increase of Lcn2 partially participates in the progression of metabolic diseases in the heart through its promotion of inflammation.

1. The characteristics and functions of LCN2

NGAL has three forms: a 25kDa monomer released from renal tubules, a 45kDa homodimer secreted by neutrophils during the inflammatory response, and a 135kDa NGAL complex with matrix metalloproteinase (MMP-9). (Romejko, Markowska, & Niemczyk, 2023).It is also known as neutrophil gelatin-associated lipid carrier protein (NGAL), 24P3, SIP 24, is referred to as LCN2 or 24P3 in mice and NGAL in humans. This protein has two cell surface receptors that bind the giant protein/glycoprotein GP330 of human LCN-2 to SLC22A17 or 24P3R of mouse LCN-1. According to reports, LCN2 binds to hydrophobic molecules such as oleic acid cholesterol, retinol, linoleic acid, platelet-activating factor, and leukotriene B4. Other inflammatory mediators are also considered potential ligands for LCN2-containing lipopolysaccharides (LPS). In addition, Lipocalin2 (LCN2) is an age-related inflammatory factor associated with many age-related central nervous system diseases and their risk factors. The expression of LCN2 in the whole body and central nervous system increases with age. It has been proven that LCN2 contributes to the pathophysiology of age-related encephalopathy by influencing various neurobiological mechanisms such as inflammation, cell death, cell survival signaling, and iron metabolism. LCN2 is expressed in normal tissues such as kidneys, lungs, bone

marrow, liver, adipose tissue, macrophages, thymus, nontumor mammary ducts, prostate, small intestine, and trachea. LCN2 does not exist in normal brain, heart, skeletal muscle, spleen, testes, ovaries, and colon, but is expressed under pathological conditions. In addition, LCN2 is an acute-phase protein that rapidly occurs when exposed to pathogens, tissue damage, and inflammatory stimuli. The expression of LCN-2 is highly elevated in many tissues and body fluids and is used for various diseases such as inflammation and metabolic disorders. The organs that include LCN-2 after onset include the liver, heart, lungs, bone marrow, kidneys, and spleen.(Jaberi et al., 2021). The expression of LCN2 in the whole body and central nervous system increases with age.(Dekens et al., 2021)

2. LCN2 and kidneys

LCN2 can be produced not only by the central and peripheral nervous systems but also by the kidneys of peripheral organs. Neutrophil gelatin-associated lipid carrier protein (NGAL) is released from the distal tubules. This biomarker can be used to locate specific fragments of damaged tubules. (Wen & Parikh, 2021)The expression of LCN2 in is relatively low and limited to specific cell types in a healthy state, but can be expressed in different ways with different cell types under different acute and chronic stimuli. LCN2 is an acute-phase protein that rapidly occurs when exposed to pathogens, tissue damage, and inflammatory stimuli. The level of LCN2 is significantly increased in various types of chronic diseases such as cancer, metabolic diseases (including obesity and diabetes), heart failure, arthritis, and chronic kidney disease.(Dekens et al., 2021)Inhibiting LCN2 may be a potential therapeutic approach to reduce FGF23 and improve the prognosis of CKD. (Courbon et al., 2021)Reducing LCN2 levels may be a treatment goal.The significant increase in NGAL levels can predict acute kidney injury after multiple cardiac surgeries, especially for BPC requiring PCI, coronary angiography, angioplasty, and contrast agents.(Marakala, 2022)

3. LCN2 and Brain

Meanwhile, peripheral LCN2 can enter the brain through the blood-brain barrier. Astrocytes are considered the main producers of LCN2 in the brain, and reactive astrocytes A1 and A2 can generate LCN2. We found that lipid carrier protein-2 (LCN2) from granulosa cells induces inflammatory activation of astrocytes, and bone marrow cells are recruited into the brain. In addition, the elevated levels of LCN2 in the patient's blood and brain metastases are closely related to the development of the disease and the low survival rate of various cancers. (Adler et al., 2023)LCN2 is associated with Alzheimer's disease, Parkinson's disease, and other central nervous system diseases.LCN2 not only plays an important role in neuroinflammation, but also involves dendritic morphology and spinal maturation. Dendrites, as a component of synapses, are closely related to memory learning. This means that LCN2 is involved in communication between neurons and glial cells. In addition, LCN2 is important for dendritic formation, and its overexpression in first generation neurons leads to abnormal synaptic conduction and reduced spike density. The neuronal adenosine receptor A1R promotes the release of LCN2, thereby activating astrocytes. These studies suggest that adenosine receptor A1R and lipoprotein calcitonin 2 may be potential targets for the treatment of AD. (Zhou et al., 2023)Compared to other peripheral immune cells, neutrophils are innate immune cells that express high levels of LCN2.(Gupta et al., 2023).LCN2 is also associated with iron deficiency anemia and is closely related to tumor metastasis.

LCN2 plays an important role in iron stability and inflammation. Its expression is induced by cytokines and lipopolysaccharides, NF-κ The B pathway is the main signaling pathway for activating LCN2 transcription. Like many other body tissues, under various acute stimuli and chronic diseases, the expression of RNA and the production of LCN2 protein in the brain are significantly increased. For example, in different animal models of acute neuronal injury and in mice with sepsis, the expression of LCN2 in the brain increases. Microarray analysis of some studies has found that LCN2 is one of the most upregulated genes in the brain and brain cells during acute inflammatory stimulation and neuronal damage. In various chronic central nervous system diseases, including neurodegenerative diseases such as multiple sclerosis (MS), AD, PD, VAD, etc., the level of LCN2 in the brain also increases. Under most of the central nervous system pathological conditions studied, astrocytes seem to be the main contributors to LCN2. Upregulation of LN2 in reactive astrocytes A1 and A2 of different types of brain injury. However, the increase of LCN2 can be generated and/or occupied by other cell types, including choroid plexus epithelial cells, brain endothelial cells, neurons, infiltrating neutrophils, and microglia.(Dekens et al., 2021)

An important factor in the reactivation of astrocytes is the cellular signaling transduction of transcription factors, including the NFkB and JAK-SAT3 signaling pathways. LCN2/Neutrophil Gelatin Associated Lipid Carrier Protein 2. Proteins and antibacterial molecules secreted by mammals. Under neuroinflammatory stress conditions, LCN2 is produced and secreted by activated microglia and reactive astrocytes in the central nervous system (CNS), leading to neuronal apoptosis.(Jung et al., 2023)

4. LCN2 and cancer

LCN2 separates iron by binding to iron chelating molecules called iron carriers, promoting cellular and systemic hypoferrosis. LCN2 can prevent iron related side effects. In xenograft tumors of cancer patients with low LIFR expression and high LCN2 expression, LCN2 neutralizing antibodies enhance isoleucine induced ferrite. The decrease in the number of LCN 2 leads to iron deficiency anemia in some liver cancers. Research has shown that apoptosis of iron cells has an inhibitory effect on tumors and metastasis. Display that tumor proteins and tumor inhibitors such as YAP, p53, and BAP1 can control ferroptosis in cancer cells. Research has shown that the LCN2 system does not exhibit significant toxicity to normal tissues under physiological conditions. LCN2 neutralizing antibodies may make tumors sensitive to radiation and immunotherapy.(Yao et al., 2021)

5. LCN2 and intradermal hemorrhage

The expression of MRNA and LCN2 proteins in brain tissue increases after cerebral hemorrhage. Proteomic analysis shows that SLC3A2 is a downstream target of LCN2, which can promote iron deficiency anemia and lead to neuronal death after cerebral hemorrhage. Finally, molecular binding and co immunoprecipitation analysis showed that LCN2 binds to SLC3A2, regulating downstream glutathione synthesis (GSH) and expression of glutathione peroxidase 4 (GPX4). Research has confirmed that the effect of dihydromycin DMY on LCN2 can provide beneficial treatment for cerebral hemorrhage. The possible mechanism is that dihydromycin DMY reverses the inhibitory effect of LCN2 on the XC system and reduces death in brain tissue. The results of this study provide a better method for the molecular level treatment of cerebral hemorrhage with dihydromycin DMY, which may contribute to the development of therapeutic targets for cerebral hemorrhage. The expression of LCN2 in astrocytes is significantly higher than that in endothelial cells or microglia.(Liu et al., 2023)

6. LCN2 and oxidative stress

Mitochondrial function is crucial for the energy metabolism of hot adipocytes. The damage of mitochondrial bioenergy in brown adipocytes is related to obesity and aging, as well as disruption of heat generation and energy balance. Phospholipids cardiac phospholipids (CL) and phosphofatty acids (PA) jointly regulate the structure and dynamics of the mitochondrial membrane, which serves as a platform for phospholipid biosynthesis and metabolism. LCN2 is an AP binding protein recruited by MAM during inflammation and metabolic stimuli. LCN2 deficiency disrupts mitochondrial fusion and division balance in brown adipose tissue of male mice, altering the acyl chain composition of mitochondrial phospholipids. LCN2 plays a role in the heat production and mitochondrial function of brown and beige adipocytes. Prevent LCN2 from interfering with the activity of signal PA by affecting its generation and operation. This in turn weakens the regulation of phospholipid metabolism enzymes that require AP activation, thereby disrupting the remodeling of mitochondrial CL phospholipids, increasing the proportion of PUFA and MUFA containing CL, CL oxidation, and ultimately leading to mitochondrial damage and dysfunction. Due to the lack of LCN2, the activation of AP can also trigger the mTOR signaling pathway, further leading to mitochondrial dysfunction and oxidative stress. This in turn leads to compensatory activation of peroxidase and increased biosynthesis of protoplasts containing LC-PPUFA. The changes in LC-PPUFA levels also include the production of liposome ligands and the PPAR required for transcription factors, such as the activation of liposome ligands α Affects mitochondrial oxidative metabolism. Finally, dysfunctional mitochondria cannot maintain redox balance, leading to increased levels of ROS and oxidative stress due to inflammation and metabolic stimuli.(Su et al., 2023)

7. Conclusion

LCN2 is a core and persistent secret that involves many neuropathological processes, including increased neuroimaging, cell death, and iron dysregulation, all of which can have a negative impact on cognitive function. In many age-related brain diseases, including AD, PD,

and VAD, the level of LCN2 in the brain is elevated. Although there have been some conflicting findings reported, an increasing number of people believe that LCN2 may exacerbate the neurodegenerative processes of many central nervous system diseases, and therefore may play an important role in various central nervous system diseases. Under risk factors, high levels of LCN2 in the central and peripheral nervous systems can lead to age-related central nervous system diseases, such as the brain gradually entering an inflammatory state, disrupting iron metabolism, and making brain cells sensitive to toxic stimuli. But the direct evidence for this possibility is still insufficient. Therefore, in future research, it is necessary to explore the mechanisms through which LCN2 effectively becomes a risk factor and its relationship with the development of age-related central nervous system diseases. In addition, the contradictory research results on the role of LCN2 emphasize that the function and function of LCN2 are complex and not fully understood. The action of LCN2 can depend on a complex combination of various factors, such as age, gender, specific disease in the study, chronic and acute nature of the disease, participating cell types, specific ligands bound by LCN2, and post translational modification status of LCN2. More research is needed to better understand the role and risk factors of LCN2 in elderly brain diseases, and to reveal the value of LCN2 as a diagnostic and therapeutic target for elderly brain diseases. In the field of geriatric science, LCN2 is an interesting factor worth considering, with a focus on elucidating the biological mechanisms of aging, leading to the development of age-related chronic diseases. The induction of iron deposition by tumor suppressor p53 can inhibit tumor development, and some mechanisms may be related to tumor development, tumor inhibition, clearance of immune system infected cells, and regulation of tissue size. In summary, there are many foreseeable opportunities to elucidate the mechanisms of iron deposition and the natural background of this form of cell death. These studies will reveal how nature acts on iron deposition to achieve purposes beyond disease and treatment. Some experimental studies on cancer models have shown that LCN2 may be an effective target, and anti LCN2 treatment reduces tumors with minimal target complications. Different strategies, such as anti LCN2 monoclonal antibodies or small interfering RNAs targeting LCN2, lead to reduced angiogenesis in breast tumors.

Research has shown that anti LCN2 antibodies can also reduce aortic aneurysm tissue damage and neutrophil infiltration. The multiple roles of LCN2 in the progressive pathophysiology of CKD remain to be studied.

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