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Lipocalin-2 Expression and Function in Pancreatic Diseases

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Abstract

Lipocalin-2 (LCN2) is a secreted molecule, expressed in various cell types, that is involved in the progression of numerous diseases and disorders. The biological functions and expression levels of LCN2 in diseases including pancreatic cancer, pancreatitis (acute and chronic), and diabetes mellitus, suggest the potential role of LCN2 as a biomarker and/or therapeutic target. However, findings on the role of LCN2 in pancreatic diseases have been contradictory. In pancreatic cancer

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and pancreatitis, LCN2 has been identified as a potential biomarker; increased expression levels in various biological specimens correlate with the presence of the disease and may be able to differentiate cancer and chronic pancreatitis from healthy subjects. LCN2 is also known to be an adipokine; it is upregulated in obesity and is a common co-factor in the development of pancreatic diseases. Emerging research suggests LCN2 is elevated in type 2 diabetes mellitus, but the exact role of LCN2 in this disease is not clear. In this review, we summarize research on LCN2 as it relates to pancreatic diseases, highlighting the discrepancies in the literature. By explaining and clarifying the role of LCN2 in these disorders, we aim to promote research in developing novel diagnostic and treatment strategies to reduce the burden of pancreatic diseases.

Keywords

Lipocalin-2; neutrophil gelatinase-associated lipocalin; pancreatitis; pancreatic cancer; obesity

Introduction

Lipocalin-2 (LCN2), also known as neutrophil gelatinase-associated lipocalin (NGAL), lipocalin 24p3, migration stimulating factor inhibitor (MSFI), superinducible protein 24 (SIP24), Ch21, α1-microglobulin related protein, uterocalin and siderocalin, is secreted from multiple tissue and cell types. LCN2 was originally isolated from the gelatinase subcellular compartment of human neutrophils supporting the innate immune responses that help fight bacterial infections[1]. Increased LCN2 expression has been associated with the innate immune system for immune cell migration, localization, infiltration, and adhesion,[2] as well as a part of the inflammatory responses related to inflammatory bowel disease,[3] psoriasis,[4, 5] metabolic syndrome,[6, 7] neurodegenerative diseases,[8-10] and cancer[11, 12].

Diseases of the exocrine and endocrine pancreas, including pancreatic ductal adenocarcinoma (PDAC), acute pancreatitis (AP), chronic pancreatitis (CP), and certain types of diabetes, have all been linked to inflammation and increased LCN2 expression. Understanding the pathophysiology that associates inflammation and LCN2 expression to disease initiation and progression could assist in the development of new treatment strategies. Among pancreatic diseases, PDAC has the worst outcome, with a survival rate of less than 9%, indicating that new, more effective diagnostic and treatment strategies are needed[13]. Both, PDAC and pancreatitis, particularly CP, are strongly associated with fibrosis and chronic inflammation[14, 15]. In AP, a single bout of the disease can alter inflammatory pathways resulting in recurrent AP or CP[16, 17]. Moreover, CP-associated inflammation and fibrosis increases the risk for developing PDAC[18, 19]. Emerging studies are now linking the gut microbiome diversity with PDAC outcomes and resistance to common treatments like gemcitabine [20, 21]. Therefore, as a regulator of immune cell migration and infiltration during inflammation, LCN2 may be one of the mediators driving increased risk and worse prognosis in patients with PDAC and other pancreatic disorders.

A comprehensive literature review was performed in order to organize and assess the state of LCN2 research and how it relates to pancreatic diseases. This review discusses current knowledge relating LCN2 function and expression with PDAC, AP, CP, and diabetes

mellitus. Additionally, the potential of LCN2 to serve as a biomarker and therapeutic target for some of these pancreatic diseases is discussed.

Physiologic Functions of LCN2

LCN2 is a 25kDa protein[22, 23] that is essential in modulating iron homeostasis[1]. It binds to three identified receptors, megalin, solute carrier family 22 member 17 (SLC22A17), and melanocortin-4 (MC4R). Megalin, also known as LDL receptor related protein 2 (LRP2), facilitates renal reabsorption of LCN2[24]. LCN2 binds specifically to SLC22A17, also known as 24p3R, and is expressed in several tissues, including pancreatic stellate cells[25, 26]. Finally, MC4R binds to osteoblast-derived LCN2 in the neurons of the hypothalamus, activating the MC4R-dependent appetite-suppressing pathway[27].

LCN2 binds ferric iron using a siderophore cofactor and serves a major role in the innate immune system[1]. Siderophore cofactors are produced by plants, fungi, bacteria,[28] and mammals[29]. LCN2 binds bacterial or mammalian siderophores, such as enterobactin,[29] which are secreted to chelate iron from host proteins during stress conditions, such as inflammation[30]. Iron scavenging by bacterial siderophores causes neutrophils in the host to secrete LCN2 to sequester the iron-siderophore complexes away from bacteria. As a result, LCN2 inhibits bacterial growth as part of the defense mechanism of the innate immune response system[31]. A variety of proinflammatory signals induce LCN2 expression, including lipopolysaccharide (LPS), and IL-1β[32]. Some of these responses are mediated through the activation of NF-KB[32].

Another function of LCN2 is to bind and transport lipophilic molecules such as fatty acids and steroids. LCN2 has a binding affinity for cholesterol, retinol, and retinoic acid[33]. For this reason, LCN2 is suggested to aid in lipid-mediated signal transductions, such as the metabolic homeostasis of thermogenesis in adipose tissue via retinoid regulation[34, 35]. As an adipokine, LCN2 expression correlates positively with adiposity, hypertriglyceridemia, hyperglycemia, and insulin resistant[36]. The critical role of LCN2 during inflammation and association with adipose tissue make it a potential target molecule for diagnosis or treatment of many inflammatory diseases and obesity-associated cancers.

LCN2 Expression and Mechanisms in PDAC

LCN2 expression has been assessed as a possible diagnostic and/or a prognostic indicator of oncogenesis in a variety of tissues[37, 38]. However, there are contradictory findings regarding the contributions of LCN2 in the pathogenesis of these cancers. For example, some studies indicate that increased LCN2 expression results in reduced invasion, metastasis, and angiogenesis of tumor cells and suppresses the process of epithelial-to-mesenchymal transition in certain cancers[39-45]. Conversely, other studies indicate poor prognosis of cancer outcomes (including PDAC), with increased levels of LCN2 associated with increased growth and survival of oncogenic cells, drug resistance, metastasis, angiogenesis, and invasion[46-51]. It is possible this apparent controversy is a result of the body trying to produce more LCN2 to reduce invasion and metastasis of aggressive cancers, however this will need to be confirmed in *in vitro* and *in vivo* experiments.

In PDAC, LCN2 expression levels begin to increase in pancreatic intraepithelial neoplasia (PanIN) lesions as early as PanIN1, and increased expression correlates with malignant progression to PDAC[52-61]. LCN2 is highly upregulated in the blood and pancreatic fluid, so it could help discriminate PDAC from other diseases and healthy subjects[60, 62]. This increased expression of LCN2 is also observed in various preclinical mouse models of PDAC[26]. However, as with other cancers, findings from research attempting to elucidate the molecular mechanisms of LCN2 in PDAC have been inconclusive and at times contradictory. Both *in vitro* and *in vivo* studies, using orthotopic and subcutaneous preclinical mouse models, have reported mixed results regarding the role of LCN2 in PDAC growth, invasion, and metastasis[43, 50, 63]. Some of these studies suggest that LCN2 serves as a pancreatic tumor suppressor,[43, 63] while others propose it is a pancreatic tumor promoter[50]. These heterogenous results could potentially be explained by the study design, as the studies did not allow for simultaneously assessing the contribution of the immune system in the progression of PDAC. To address this concern, our laboratory used a genetically engineered mouse model (GEMM) of PDAC and crossed it with an *Lcn2* null mice to show that lack of *Lcn2* decreased inflammation and fibrosis of the tumor microenvironment[26]. Moreover, whole body deletion of *Lcn2* in this GEMM prolonged survival of mice predisposed to develop PDAC due to Kras expression and feeding of a high-fat diet[26].

In addition to regulating inflammation in the tumor microenvironment, LCN2 expression may also modulate metastasis and angiogenesis. LCN2 depletion is observed in poorly differentiated PDAC tissue (mesenchymal-like), and is thought to be necessary for invasion and metastasis[40, 41, 43, 44, 53]. Relative to these observations, epidermal growth factor decreases LCN2 expression via NF-KB inhibition in PDAC[63]. This down regulation of LCN2 is brought about by the activation of the EGFR/MEK/ERK signaling pathway, which subsequently inhibits E-cadherin, a regulator of the epithelial-to-mesenchymal transition (EMT), along with a reduction of NF-KB activation, another regulator of EMT[39, 63]. Alternatively, the NF-KB p50 protein and the nuclear protein IKBζ form a transcription complex on the *Lcn2* gene promoter and generate *Lcn2* mRNA for increased expression[64]. Since LCN2 may be either pro- or anti- oncogenic depending on the type of cancer, it will be critical for future research to establish the mechanism that causes the transition between excess LCN2 secretion and an inhibition of LCN2 expression in PDAC.

In the tumor microenvironment, LCN2 inhibits angiogenesis by reducing VEGF expression, leading to a hypovascular tumor environment[44, 65, 66]. Typically, preventing angiogenesis inhibits tumor growth; however, in PDAC, the hypovascular environment is detrimental as it limits effective delivery of chemotherapy. Therefore, inhibiting LCN2-induced hypovascularity, possibly through antibody neutralization or directed small molecule inhibition treatment could enhance treatment effectiveness. Altering the expression of, or preventing LCN2 secretion may be key to future therapeutic approaches for PDAC.

Aside from therapies, clinical research on LCN2 focuses on whether it can be used as an early biomarker of PDAC or for staging of the cancer. LCN2 expression has been assessed as a diagnostic biomarker in urine, serum, bile, pancreatic fluid/juice and fluid from pancreatic cysts (Table 1).[26, 43, 52-54, 56, 60, 61, 67, 68]. One group showed that LCN2 in combination with miR-196b and TIMP1 is 100% specific and 100% sensitive in

distinguishing patients with PanINs and stage I PDAC from healthy subjects amongst a cohort of high risk individuals; however, this combination did not perform as well in discriminating PDAC from CP (sensitivity 50%, specificity 80%)[54]. It has been suggested that effective use of LCN2 as a diagnostic biomarker for PDAC can be improved by comparing serial levels in urine samples, with doubling in concentration being indicative of PDAC[69]. Further studies are needed to assess temporal trends in other fluids, including serum and bile.

LCN2 Expression in Acute and Chronic Pancreatitis

AP is usually a self-limited disorder where duration and degree of organ failure determines the severity of the disease, with the most severe cases resulting in multi-systemic organ failure and death[70]. Expression of LCN2 has been associated with increased severity of AP; however these findings are debatable[71-73]. Some studies suggest urine LCN2 is an effective early marker for AP[74-76]. In particular, these studies show a strong correlation between LCN2 elevation and severity of AP. Other studies looking at the physiologic changes occurring after AP has resolved found a delayed increase of LCN2 expression in AP patients when alcohol was the etiology [77]. Elevation in LCN2 was particularly noted in obese subjects with excess abdominal adiposity, but only after AP had resolved[77]. This delayed elevation in LCN2 may be associated with a lingering inflammatory response and may be involved in the progression to recurrent AP (RAP) or CP. A study examining the expression of LCN2 across various etiologies of AP and controlling for adiposity is needed to better understand the role of LCN2 in the progression of these diseases.

Acute kidney injury (AKI) is a somewhat common complication seen in moderately severe and severe AP, and associated with worse clinical outcomes including increased length of stay. Increased LCN2 expression has been associated with development and severity of acute kidney injury (AKI)[73]. LCN2 is currently being assessed for applicability as an biomarker of AKI since it may become elevated prior to changes in serum creatinine, the current clinical standard marker for AKI[72,73,78,79]. This could be particularly helpful in the subset of AP patients who develop delayed organ failure. Therefore, LCN2 may have a potential role for predicting both long term and acute progression of AP.

CP is a progressive and degenerative disease with symptomatic pain and inflammation, characterized by an irreversible and deleterious effect on the exocrine function. CP-associated inflammation is caused by an infiltration of immune cells like T-cells, particularly $CD4^+$ and $CD8^+$ T-cells,[80] and macrophages and progressive fibrosis of the pancreas[81]. CP patients have an increased lifetime risk for developing PDAC with a standardized incidence ratio of 15-16 times higher than the general population, possibly due to the similarities in inflammatory infiltration and fibrosis between the two diseases[82].

No biomarkers are clinically available to differentiate CP from other gastrointestinal disorders like AP and PDAC. Due to the nature of CP being associated with increased, chronic inflammation and immune cell filtration, several groups have looked into whether LCN2 can be used as a biomarker for CP. LCN2 is elevated in CP subjects compared to healthy individuals, as measured in pancreatic fluid, urine, and bile[52, 67]. Some studies

indicate LCN2 is elevated in both CP and PDAC and proposed it is due to overlapping mechanisms of chronic inflammation[52-54, 60]. However, other studies assessing LCN2 in urine or bile collected intraoperatively suggest LCN2 concentrations could differentiate CP and PDAC[67]. Being able to differentiate CP from AP or patients with other gastrointestinal disorders by assessing concentrations of LCN2 in the aforementioned studies is a large step towards potentially using LCN2 as a biomarker in the clinic. However, there is still a need for several large, multi-center studies to determine whether LCN2 can be used as an effective biomarker for detecting early stages of CP where most diagnostic uncertainty exists. Additionally, although LCN2 is elevated in CP, there is a lack of research on the exact role of LCN2 in the development or persistence of CP and whether LCN2 blockade could be a therapeutic target for CP.

LCN2 Expression in Obesity-Related Pancreatic Diseases

There is a strong link between obesity and diabetes mellitus, AP and its severity, and PDAC[83]. Elevation of LCN2 has been implicated in the development of chronic low-grade inflammation associated with obesity[84]. Obesity is also correlated with increased immune system activation, with elevated serum and visceral adipose tissue concentrations of LCN2[84]. Recent studies have demonstrated that LCN2 can predict early stages of type 2 diabetes mellitus in obese women[85]. In both children and adults, an increase in LCN2 expression has been positively correlated with increased weight, BMI, waist-to-hip ratio, waist circumference, percent body fat, and serum concentrations of insulin, glucose, and triglycerides, while being negatively correlated with high-density lipoproteins[7, 86, 87]. Several studies have linked increased LCN2 expression to insulin resistance and sensitivity, glucose uptake, and obesity[88, 89]. In mice, LCN2 expression in adipocytes and hepatocytes was regulated by obesity, and elevation in *Lcn2* enhanced insulin resistance[90].

Diet appears to play a critical role in LCN2 function and influences biological processes. A recently published analysis of *Lcn2* in mice concluded that under normal diet the *Lcn2* knockout mice phenotype and physiology were virtually identical to controls[91]. When provided a high fat diet, *Lcn2* null mice exhibited several physiologic differences compared to controls including, generation of more brown adipose depots, increased oxygen consumption, increased diet consumption, and reduced weight gain compared to a normal diet control or wild type mice fed a high fat diet. These findings underscore the link between LCN2, obesity, and metabolism[91]

Medical professionals often recommend changes in diet and increased exercise to reduce obesity and risk of obesity-related diseases. However, in a study on the effects of obesity in Korean women, increased exercise was insufficient to reduce serum LCN2 levels[92]. This is unexpected since other studies indicated exercise can reduce inflammation, even in obesity, in both men and women[93-95]. Future studies should address whether exercise before, during, and/or after inflammatory pancreatic disease alters circulating LCN2 as well as other inflammatory cytokines and adipokines or whether the changes are related to ethnicity. This information will be essential to clinicians when developing patient-specific plans for reducing risk for obesity-related pancreatic diseases, and ultimately to improve patient outcomes in these diseases.

Conclusions

LCN2 expression is increased in AP, CP, pancreatic cancer, and diabetes mellitus (Figure 1); however, the underlying mechanisms and its function in initiation and progression of these diseases remains unclear. Changes in LCN2 expression may be a useful early diagnostic biomarker, but further validation using samples derived from larger multi-institutional cohorts is needed. Since LCN2 has a role in the innate response of bacterial infections, further investigations should consider the potential impact of subsets of gut or local pancreatic microbiota to initiate LCN2 secretion. Understanding the functions of LCN2 in AP and CP will be critical to better understanding disease progression, and targeting immune-associated proteins like LCN2 may potentially be a therapeutic option. Additional studies are needed understanding the diagnostic and therapeutic of LCN2 expression in PDAC. Experiments using GEMMs of PDAC will likely be necessary, because PDAC is typically advanced at the time of diagnosis making it difficult to understand the molecular mechanisms of tumor pathogenesis and progression. Further research into the function of LCN2 will further guide our understanding of its potential use as a diagnostic biomarker and potential therapeutic target, and hopefully create new opportunities to improve the care of patients with pancreatic diseases.

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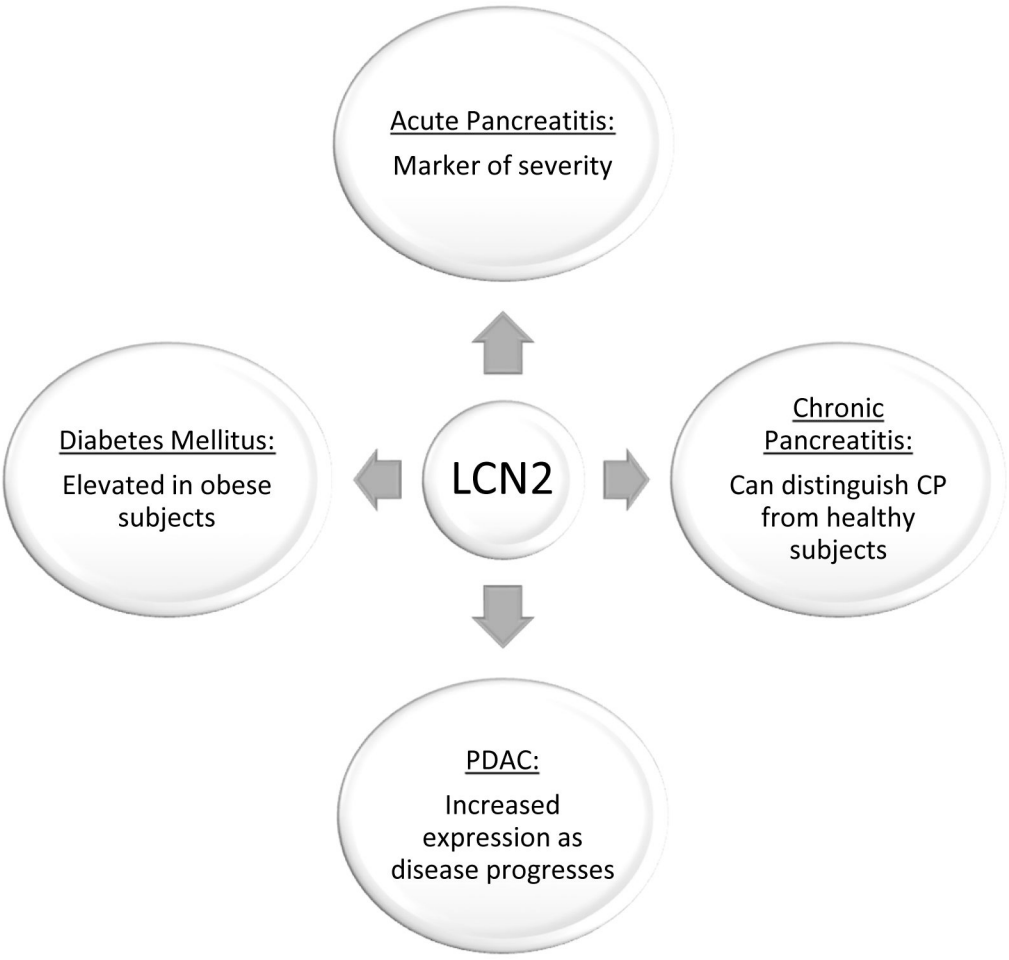

Figure 1:
Summary of the Role of LCN2 in Pancreatic Diseases

Table 1:

Summary of LCN2 Expression Levels in Human Subjects with Pancreatic Diseases.

Pancreatic Disease	Biospecimen	Detection Method	LCN2 Expression (Summary)	Year + Ref.
PDAC	Tissue (core biopsy)	RT-PCR IHC	↑ in tumor tissue vs. normal tissue	2006 [61]
	Tissue	IHC	Predominantly expressed in PanIN-1 and PanIN-2 lesions	2008 [43]
	Tissue	IHC	↑ with increasing PanIN score	2008 [53]
	Serum	ELISA	↑ in PC with diabetes ↓ after surgical removal of PDAC	2013 [56]
	Plasma	ELISA	↑ in PDAC compared to healthy controls	2013 [60]
	Cyst Fluid	ARCHITECHT Analyzer	↑ in inflammatory cystic group over cystic neoplasm	2018 [68]
	Serum	ELISA	↑ in familial pancreatic cancer	2018 [54]
CP vs. PDAC	Plasma	ELISA	↑ in CP and PDAC patients, but could not differentiate CP from PDAC	2013 [52]
	Urine Bile	ELISA	Differentiated PDAC from CP	2016[67]
	Serum + Plasma	ELISA	↑ in PDAC compared to CP and normal	2017 [26]
AP	Serum	ELISA	↑ between 24 and 48 hours and differentiated mild vs. severe AP	2010 [71]
	Serum	Fluorescent Immunoassay Triage®	↑ compared to ventilated patients without pancreatitis	2013 [75]
	Urine Serum	ARCHITECHT Analyzer ELISA	Mild ↑ in urine between 24 and 72h No significant change in serum	2016 [72]
	Serum	ELISA	↑ but no significant different between mild and severe	2016[73]
	Urine	Urinalysis	↑ correlates with severity	2016 [76]
	Serum	MILLIPLEX MAP human metabolic magnetic beads	↑ after AP Mild ↑ associated with RAP, but not significant	2017 [77]
Diabetes Mellitus	Serum		↑ in type 2 diabetes mellitus	2013[56]

AP, acute pancreatitis; CP, chronic pancreatitis; ELISA, enzyme-linked immunosorbent assay; IHC, immunohistochemistry