REVIEW ARTICLE

NGAL: An Upcoming Biomarker of Interest

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Abstract

Aim: Neutrophil gelatinase-associated lipocalin (NGAL) performs important functions in the body. It has the potential to act as a diagnostic and prognostic biomarker for various diseases.

Background: The role of NGAL has been well explored in acute and chronic kidney diseases (CKDs). It is considered a maker for acute kidney injury (AKI). Its role in other diseases has also been increasingly reported.

Results: Neutrophil gelatinase-associated lipocalin takes part in the pathogenesis of several diseases, besides renal diseases, like cardiovascular diseases, inflammatory disorders, cancer, diabetes, etc. by a variety of mechanisms. Its levels have been correlated with the severity in most of the diseases.

Conclusion: Neutrophil gelatinase-associated lipocalin can act as a biomarker in different diseases though, its potential is yet to be explored to the maximum.

Clinical significance: Estimating the levels of NGAL in body fluids will help in making an early diagnosis, assessing the severity of the disease, establishing a prognosis, and improving the overall management of different diseases.

Keywords: Biomarker, Diseases, Neutrophil gelatinase-associated lipocalin, Lipocalins.

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Introduction

Lipocalins are a large group of smaller proteins, which are mainly extracellular. Structurally, lipocalins show eight β strands that form β barrel called the calyx. The function of the calyx is to bind and transport low molecular weight molecules, through which lipocalin exerts its biological activity. Some examples are retinol-binding proteins (RBPs), which attach and deliver vitamin A; the lipocalin Alpha 1-microglobulin (A1M) which degrades heme, and nitrophorin-type lipocalins, which aid in the transfer of heme groups that have been complexed with nitric oxide.[1]

By comparing the similarities in their protein sequences, two groups of lipocalins can be distinguished. The first group comprises retinoic acid-binding proteins (RABPs), RBPs, fatty acid-binding proteins (FABPs), and peripheral myelin proteins (PMPs). The second group contains α-1 acid glycoprotein (A1AGs), lipocalins LCN1, LCN2, LCN6, LCN8, LCN9, LCN10, LCN12, and LCN15 and odorant binding protein (OBP).[2]

Human NGAL, a glycosylated protein belonging to the lipocalin family has a molecular weight of 25 kDa.[3] Due to its structural property, earlier, it was found to have an immunological activity against bacteria by capturing siderophores (such as bacterial enterochelin and mammalian endogenous catechols), which has a strong affinity for iron, leading to deficiency of iron and subsequently halting bacterial cell growth. The latest evidence shows that NGAL may be an indicator of disease conditions in overall acute and chronic pathological states and in inflammatory, metabolic, neurologic, cancer, and specifically renal diseases. It has been well established that in cases of acute renal injury, urine and blood levels of NGAL monomer increase.[4]

Different isoforms of NGAL have been identified. A 30 kDa isoform, a 46 kDa homodimer having a disulfide bond, and a 130 kDa heterodimer attached to the zymogen precursor of the matrix metalloproteinase-9 (proMMP-9) have been described. NGAL was originally isolated from neutrophils, while it is also expressed by other tissues, namely, renal, hepatic, and vascular cells (endothelial, smooth muscle cells, and macrophages in atherosclerotic plaques), as well as cardiac muscle cells.[4]

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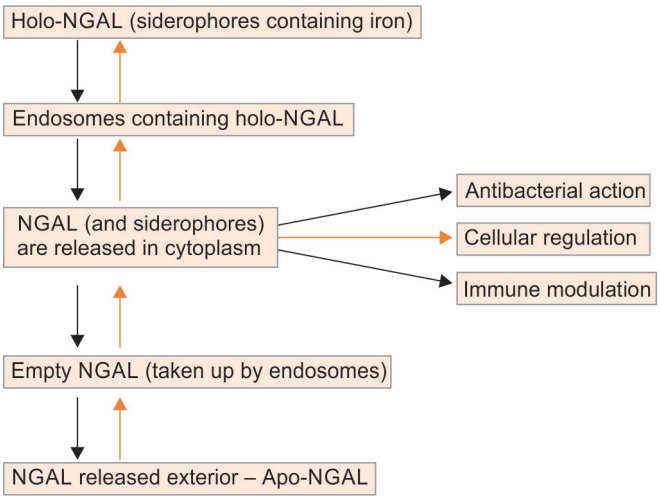
Review Methodology

For conducting the review article as per Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, the related studies were searched using academic search engines such as Google Scholar, Educational resources information center, Refseek, etc. The recent studies addressing the role of NGAL as a biomarker in different disorders and reports were included for the review.

Flowchart 1: Flowchart showing antibacterial activity of NGAL by scavenging iron



Functions of Lipocalins

Antibacterial Activity

Neutrophil gelatinase-associated lipocalin exerts its antibacterial defense function by two mechanisms. Firstly, by binding to the siderophores by which bacteria absorb extracellular iron and scavenge it. Tubular cells act on the NGAL–Fe–siderophore complex by raising the cytoplasmic iron content and by upregulating the iron-dependent processes (Flowchart 1).

The second mechanism of action of NGAL is by its attaching to eukaryotic ligands such as catechol which otherwise form a catechol–Fe complex that generates oxidative stress. Additionally, the transportation of iron from the inside of the cell to the outside is carried out by free NGAL.

In addition to having antibacterial properties, NGAL induces epithelial proliferation in several organs, including the kidney, *via* an unidentified iron-independent mechanism.[5] Acute kidney injury causes increased NGAL expression, which causes elevated levels in urine and serum in humans as well as animals. The majority of research reports suggest that NGAL is protective against AKI. However, NGAL might play a harmful effect in the course of CKD.[6]

Immune Modulation

The plasma levels of several proteins fluctuate during the acute phase response, which is a complicated physiological response against stress and inflammation. Positive acute-phase proteins (APPs) are the ones whose concentration is raised during acute events. These include pregnancy protein 14 (PP14), the lipocalins NGAL, AGP, and A1M. The lipocalin RBPs is one of the negative APPs. Positive acute-phase proteins perform several tasks that are comparable to lipocalins, including the transport of proteins, iron, and other substances, as well as anti-inflammatory activity and the prevention of tissue damage. Another lipocalin, the C8γ, is a component of the human complement's membrane-attack complex.[7]

A well-studied plasma protein called lipocalin A1M inhibits the immune system.[8,9] It is a positive APP with elevated hepatic expression, but its plasma levels remain rather constant throughout inflammation. Also, A1M reduces polyclonal proliferation of cultured lymphocytes induced by an antigen which is found to be partial at normal plasma concentrations and complete at 10–20 times higher levels.[10] The synthesis of complexes with IgA, fibronectin, and A1M aids in the regulation of the immune system. The increased protein production in response to interleukin-6 stimulation (produced by macrophages and T-lymphocytes) could be a result of a negative feedback mechanism. Additionally, A1M inhibits the chemotactic attraction of neutrophil granulocytes by a cytokine concentration gradient created by activated leucocytes and blocks the spontaneous movement of neutrophil granulocytes *in vitro*.[7]

The lipocalin AGP, also known as orosomucoid, is present abundantly in plasma. As a positive APP, AGP has shown many immunoregulatory properties such as the ability to inhibit platelet aggregation, facilitate wound healing, inhibiting the activation of neutrophils and phagocytes, along with several non-specific immunosuppressive properties.[11,12]

Cell Regulation

Many lipocalins show their role in cell regulation. Out of them, the first to be studied was quiescence-specific protein (QSP). Confluent cells, the cells which are stimulated by growth factors or hormones, express the QSP protein in a density-dependent manner. Hormone-stimulated cells synthesize a large amount of the protein, although the levels are much low when compared with the quiescent cells.[13]

Another lipocalin named probasin participates in cell regulation and was initially separated from the nuclei of rat dorsolateral prostate epithelial cells.[14]

A lipocalin named purpurin is present almost specifically in retinal neural cells. It is a both retinol and glycosaminoglycan binder that regulates cell differentiation, adhesion, and survival.[15]

Prostaglandin Syntheses

The main compound involved in the formation of prostaglandin 1 (PGD_1) in the brain is glutathione-independent PGD_2 synthase which accounts for over 90% of activity in the rat. In the presence of different thiol compounds, it catalyzes the conversion of PGH_1 into PGD_1. Also, PGD_1 is a crucial PGD in mammalian brains that acts as a neuromodulator and a trophic factor. Among the lipocalins, PGD synthase has a distinct enzymatic activity.[16]

Olfactory and Gustatory Proteins

Odorant binding proteins are unique lipocalins that are linked to olfactory tissue and have a high level of specificity in their binding to odorant molecules. It has been speculated that two lipocalins, which are exclusively expressed in the vomeronasal and posterior glands of the mouse nasal septum, function in the chemoreception of small lipophilic pheromones.[17] Similar functions are carried out in salivary secretions by another lipocalin, which is abundantly produced by the tiny acinar von Ebner's salivary glands of the tongue.[18]

Pheromone Activity

Mouse urinary protein (MUP), which is expressed in a variety of mouse secretory organs and is the main protein present in mouse urine, is a lipocalin. The liver is the main location for MUP synthesis. The idea that MUP functions as a pheromone transporter are supported by the sex-dependent production of MUP (adult male mice secrete 5–20 times as much MUP as do females) and its capacity to bind a variety of odorant molecules.[7]

Aphrodisin, a lipocalin that is also released by vaginal tissue and the Bartholin's gland, makes up the majority of the macromolecular

components of hamster vaginal discharge. These secretions evoke a copulatory response in male hamsters operating through the vomeronasal organ.[19]

Diagnostic Methods for Estimation of NGAL

Serum NGAL is measured commonly by enzyme-linked immunosorbent assay (ELISA), chemiluminescent immunoassay (CLIA), and radioimmunoassay (RIA) methods.[20] All techniques have been reported to assess NGAL accurately. The CLIA method is faster these methods while ELISA is a cost-effective and simpler method. The sensitivity of RIA is higher than ELISA.[21]

Role of NGAL in Different Diseases

Kidney Diseases

For early detection of both acute renal injury and CKD, there is an urgent need for biomarkers. In both conditions, early intervention using biomarkers can significantly improve the prognosis. The currently available biomarkers fail to detect them at an early stage with sufficient accuracy.[6]

Acute renal injury solely complicates 7.2–20% of hospitalized patients and 13–78% of intensive care unit (ICU) patients. Acute kidney injury and critical illness, together, have a high fatality rate and demonstrate a bad prognosis for patients. In the last few decades, serum creatinine (SCr) is used to diagnose AKI but it is a functional marker and is not the best means to diagnose AKI. It gets affected by variables like age, sex, muscle mass, drug use, and dietary habits. Furthermore, SCr is not found to increase until more than 50% of kidney function has been lost, delaying the detection and treatment of AKI.[22]

In animal models of ischemia or nephrotoxic AKI, NGAL expression is significantly increased in the kidney. Its levels can be detected in the plasma of patients as early as 2 hours after the injury, attaining a peak at around 6 hours, and remaining elevated for as long as five days before starting to decrease.[22] The proteolytic activity of gelatinase B on collagen is increased as a result of the inhibition of its breakdown by NGAL. In both blood and urine, the concentration of NGAL is minimal (approximately 20 ng/mL) at a steady state. The main regulators of NGAL concentration at steady state, neutrophil generation, and renal clearance, are reflected in these concentrations. NGAL levels rise and become noticeably elevated in individuals receiving chronic dialysis, as renal function deteriorates.[23]

Cardiovascular Diseases and Inflammation

By attaching to chemotactic peptides, NGAL acts as a scavenger in inflammatory regions and controls inflammation. The central part of NGAL in atherosclerosis is seen to be clustered with MMP-9, an endopeptidase, that controls cellular breakdown in atherosclerotic plaques. By combining with MMP-9 to form a complex, NGAL extends the proteolytic activity of MMP-9 to collagen. This increases the plaque's risk of rupture, which ultimately leads to myocardial infarction. Neutrophils are shown to express twice as much NGAL in patients with abdominal aortic aneurysms as they did in healthy controls. Cardiomyocyte NGAL concentration rises in heart failure patients and may play a role in MMP-9-mediated myocardial remodeling. Findings of a potential association between NGAL and cardiovascular disease also support NGAL's participation in atherosclerosis.[24] Increased NGAL appearance was associated with unstable plaque phenotype in atherosclerotic lesions, which is characterized by high lipid content, a greater number of macrophages, less smooth muscle cells, and intraplaque bleeding.[24]

Neutrophil gelatinase-associated lipocalin is an APP, which has been associated with elevated interleukin (IL-6 and IL-8) levels in human atherosclerotic tissue. Clinical investigations have also shown a correlation between plasma NGAL and inflammatory markers.[26]

Patients who have experienced an acute cerebrovascular accident have been discovered to have elevated serum levels of NGAL, which continue to be elevated for up to a year. Hypertensive patients show higher NGAL levels than those with normal blood pressure, and these levels correlate with renal function, age, and the severity of hypertension. When compared to control subjects with normal arteries, patients with angiographically diagnosed coronary artery disease have been found to have considerably higher serum NGAL levels.[26]

Cancer

When granulocyte precursors mature in the bone marrow, myelocytes and metamyelocytes exclusively produce NGAL.[28] Recent research has suggested that NGAL may have an important role in cancer and that it may possess both anti-oncogenic and pro-oncogenic properties.[29] As seen in cancers of the colon, ovary, and pancreas, its anti-tumor activity may be linked to the inhibition of various pro-neoplastic factors such as hypoxia-inducible factor-1a (HIF-1a), the HIF-1a-dependent vascular endothelial growth factor (VEGF), and focal adhesion kinase (FAK) kinase.[30–32] While NGAL's reported oncogenic effect is mostly attributed to its ability to form a complex with MMP-9, NGAL/MMP-9 complex. By the formation of the complex, MMP-9 gets protected from auto-degradation and can exert its gelatinolytic activity, increasing the invasiveness of cancer tissue.[33] Through this, it has been shown that NGAL may encourage the growth of a variety of cancer tissues.[33]

Quantitative assessments of the amounts of NGAL protein and mRNA in blood, urine, and tissues indicate that NGAL is overexpressed in malignancies that are not caused by microbes, such as bladder, liver, lung, breast, ovarian, endometrial, pancreatic, and colorectal cancers.[4] The unusually elevated levels of NGAL in the majority of malignancies seem to be significantly linked with disease severity and decreased survival. It has been proposed to be a significant diagnostic biomarker for late-stage or recurrent malignancies of the ovary, pancreas, stomach, and intestines. Neutrophil gelatinase-associated lipocalin does not seem to have diagnostic value for some malignancies but may be useful for predicting prognosis in patients with metastases. For instance, NGAL is not a reliable biomarker for the diagnosis of renal cell carcinoma, but it may be useful in determining the best course of treatment for patients with the metastatic illness. The aggressiveness of breast, kidney, stomach, anaplastic thyroid, and oral cancer is frequently linked to the expression of the NGAL.[4] The NGAL status may help determine the tumor stage in endometrial cancer patients before opting for surgical treatment.[34]

Leukemias

As hematopoietic progenitor cells undergo neoplastic transformation, leukemias (both acute and chronic lymphoid or myeloid types) are categorized as clonal diseases. These disorders are characterized by the survival and growth of clonal progenitors, cell dispersion from the bone marrow into the blood and peripheral organs as well as chemotherapy resistance.[4]

Blood from patients with acute lymphoid leukemia (ALL), acute myeloid leukemia (AML), and chronic lymphoid leukemia (CLL) contains the NGAL complex.[4] In AML patients, those with a good prognosis exhibit higher levels of NGAL mRNA expression in the bone marrow than those with a bad prognosis. Additionally, patients with the wild-type FLT3-ITD sequence and higher NGAL mRNA expression levels in the bone marrow have improved prognoses. It is unknown whether NGAL (dimer and/or monomer, free and complexed) in the blood of patients with AML, ALL, or CLL has prognostic significance or not.[35]

Imatinib reduces the constitutive tyrosine kinase activity of p210 BCR–ABL in the cases of CML and relieves the symptoms brought on by hyperproliferation.[36] Additionally, NGAL serum levels are noticeably higher in CML patients than in healthy people. In CML patients receiving imatinib therapy leading to complete molecular remission, serum NGAL levels are seen to be decreased and are much less as compared to those having the full-blown disease.[37] These results strongly support a functional connection between NGAL and BCR-ABL and suggest that NGAL is a valuable marker of CML's response to therapy.[4]

Strength, Limitations, and Future Directions

The review has described the important functions of NGAL including its structure and mechanism of action, besides its role as a biomarker, by consulting a substantial number of pertinent studies. The review could have projected the competence of NGAL as a biomarker in a better way with a robust search selection, data collection, statistical analysis, and bias assessment process. These processes would make part of our future project.

Conclusion

Neutrophil gelatinase-associated lipocalin is a lipocalin performing several important biological functions in the body. Its levels have been found associated with many acute and chronic diseases including kidney, inflammatory, cancer, and cardiovascular diseases. Estimation of levels of NGAL in the blood and urine of patients may help healthcare professionals in diagnosing, and assessing the severity of the disease for better prognosis.

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