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REVIEW

Neutrophil gelatinase-associated lipocalin and innate immune responses to bacterial infections

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Abstract Neutrophil gelatinase-associated lipocalin (NGAL), an essential component of the antimicrobial innate immune system, is present in neutrophils and multiple other tissues. It prevents iron acquisition by microorganisms by sequestering iron-loaded bacterial siderophores. NGAL also modulates neutrophil functions. Its production is inducible following Toll-like receptor 4 activation and release of pro-inflammatory cytokines. NGAL is employed clinically in the diagnosis of acute kidney injury and may be useful in general in the differential diagnosis of a bacterial-mediated infectious process. Elevated levels of NGAL have been detected in the blood of patients with bacterial urinary tract infection, community-acquired pneumonia, sepsis, as well as in the cerebrospinal fluid and peritoneal fluid of patients with bacterial meningitis and peritonitis. Some bacteria have developed resistance to NGAL-mediated iron sequestration by production of modified siderophores that are not recognized by NGAL.

Keywords Neutrophil gelatinase-associated lipocalin · Lipocalin 2 · Innate immunity · Infectious disease

Introduction

Iron is an essential micro-element for bacteria, fungi and mammals. The iron concentration required for growth of most bacteria in a human host is much higher than the concentration of free available iron [1]. To overcome this deficit, many bacteria secrete iron-binding proteins called siderophores, which due to their high affinity for iron "steal" Fe3+ from host iron-binding proteins such as lactoferrin and transferrin [2]. To prevent bacterial iron acquisition via siderophores, mammals employ the siderophore-binding protein neutrophil gelatinase-associated lipocalin (NGAL), also known as human neutrophil lipocalin or lipocalin 2. NGAL belongs to the lipocalin family, a diverse group of small proteins that bind small mainly hydrophobic molecules such as iron, fatty acids, prostaglandins, steroids and matrix metalloproteinases [3]. NGAL can be found as a monomer, a homodimer or as a heterodimer, disulfide linked with matrix metalloproteinase (MMP)-9 [4, 5]. NGAL is constitutively present in peroxidase negative granules of neutrophils, co-localized with lactoferrin, and is released following neutrophil activation [6, 7]. It appears early in the granulocyte differentiation pathway and thus is a marker of neutrophil formation [8]. In addition, NGAL can be found in a large number of tissues such as colon, uterus, trachea, lung, stomach, prostate and salivary gland [9]. Its concentration has been shown to increase in kidney tubular cells, intestinal epithelial cells, stomach cells and hepatic cells in response to a variety of noxious stimuli, which include infection or ischemia [10–13]. In this review, we highlight the role of NGAL in antimicrobial immunity against human pathogens at diverse body sites, describe how some bacteria evade NGAL-mediated effects, and highlight potential avenues for future investigation.

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Biological functions of NGAL

In vitro and in vivo experiments have confirmed that NGAL is an essential component of antimicrobial innate

Table 1 Summary of antimicrobial effects of NGAL

Property	References
1. Sequesters iron-loaded bacterial siderophores	[16]
2. Sequesters iron-loaded L-norepinephrine	[17]
3. Promotes neutrophil adhesion and extravasation	[21]
4. Acts as chemoattractant for neutrophils	[20, 21]
6. Promotes phagocytosis and bacterial killing by neutrophils	[20]
7. Promotes neutrophil maturation	[20]
8. Activates CD4+/FoxP3+ T regulatory cells	[22]

immunity, especially during the early stages of infection. NGAL-deficient mice display increased susceptibility to infections and an inability to clear invading bacteria [14, 15]. The main bacteriostatic function of NGAL is its binding and sequestration of bacterial siderophores, thus depriving bacteria of iron [16]. NGAL also deprives bacteria from iron acquisition from catecholamines by strongly binding to iron-loaded norepinephrine [17]. NGAL-ferric siderophore complexes interact with megalin, a multiligand receptor present on host cells and are endocytosed and degraded in the cytoplasm [18]. A second receptor for NGAL is 24p3R, which induces apoptosis in response to low intracellular iron concentrations [19]. The role of NGAL in antimicrobial innate immunity is not limited solely to iron deprivation. NGAL also modulates several neutrophil functions. Neutrophils derived from NGAL-deficient mice failed to phagocytose and kill bacteria, did not extravasate to infection sites, and had impaired chemotaxis and adhesion [20, 21]. Moreover, there is in vitro evidence that NGAL can link innate and adaptive immunity. NGAL increases in an iron-independent manner the expression of HLA-G (a HLA class I molecule involved in tolerance) on CD4+ T lymphocytes. Iron-bound NGAL also activates CD4+/FoxP3+ regulatory T lymphocytes, suggesting its possible involvement in modulating cell-mediated immunity [22].

Other biological functions have also been attributed to NGAL. It has antioxidative properties [23], promotes apoptosis [19], and participates in kidney organogenesis by inducing epithelial cell development [24]. NGAL has a documented role in the development of cardiovascular disease [25] and is currently promoted as a "troponin-like" marker for the early diagnosis of acute kidney injury (AKI) [26, 27], although there are recent concerns regarding this property, especially in an intensive care unit (ICU) setting [28]. There is no clear consensus regarding the role of NGAL in tumorigenesis and tumor progression; studies have identified both pro- and anti-tumor properties of NGAL [29]. The antimicrobial properties of NGAL are summarized in Table 1.

Under some conditions, NGAL-related effects may be detrimental to antimicrobial host defenses. NGAL stabilization of MMP-9 has been shown to aggravate *Salmonella typhimurium*-induced colitis, by promoting degradation of the extracellular matrix [30]. Increased levels of NGAL during an infection may also induce anemia since it suppresses red blood cell production by inhibiting hematopoietic stem/progenitor cell differentiation and inducing apoptosis [31, 32].

Gene expression and regulation

Initial cloning and sequencing of the NGAL gene identified a 3696 base pair coding region, organized into 7 exons and 6 introns, along with a number of possible cis acting elements within the promoter region, which included a binding site for NF-kappaB (NFκB) [9]. NGAL gene expression is strongly induced in human epithelial cells by interleukin (IL)-1β. Its induction is dependent on the presence of the NFκB transcription factor and the de novo synthesis of the IKappaB zeta cofactor, which in turn interacts with the p50 subunit of NFκB [33–35]. Secretion of IL-17 by Th17 + CD4 lymphocytes stabilizes the ikappaB zeta transcript and may enable a tumor necrosis factor (TNF)-*a*-dependent up-regulation of NGAL gene expression [36]. This is supported by the observation that NGAL gene transcription within intestinal epithelial cells is induced by the synergistic action of IL-17 and IL-22 [37]. Likewise, in a murine model of oral candidiasis, the NGAL gene was strongly induced by IL-17 within infected mucosal tissue [38]. Also, NGAL gene expression has been induced in adipocytes after exposure to interferon (IFN)-γ [39]. Furthermore, Toll-like receptor (TLR) 4 activation has been shown to be essential for NGAL gene induction by lipopolysaccharide (LPS) [33, 34].

Central nervous system

In murine models of systemic endotoxemia induced by intraperitoneal injection of LPS, NGAL expression was up-regulated in brain tissue and was located mainly in endothelial cells of blood vessels, microglia, epithelial cells of choroid plexus and astrocytes [40–42]. NGAL promotes microglial activation by stimulating their M1 phenotype, which results in the production of pro-inflammatory cytokines; their conversion to the M2 phenotype associated with phagocytosis and wound repair is inhibited. NGAL knockout (KO) mice display lower levels of glial activation and related neurotoxicity, with a positive net effect on motor behavior and cognitive function [42, 43]. Also, NGAL acts in an autocrine manner, regulating the function

of astrocytes; more specifically, it promotes a pro-inflammatory astrocyte phenotype and controls their migration [44, 45].

In clinical settings, patients with acute meningitis of bacterial origin have higher cerebrospinal fluid (CSF) levels of NGAL compared to patients with acute viral meningitis [46]. A separate study confirmed these results and reported a significant correlation of CSF NGAL with CSF values of polymorphonuclear leukocytes, total white blood cells, erythrocytes and total protein [47]. Pending additional confirmatory studies, these clinical findings suggest that CSF NGAL may be a promising marker for the early identification of bacteria-mediated acute meningitis.

Respiratory system

In normal human lung tissue, NGAL is present constituently within tracheal goblet cells and type II pneumocytes [33]. In an experimental murine model of gram-negative bacterial pneumonia, expression of NGAL from these cells was induced after exposure to *Escherichia coli,* contributing along with migratory neutrophils, to the increased levels of NGAL within the infection site. In the same model, a higher bacterial load was reported in NGAL KO mice, suggesting its important role in the clearance of *E. coli* and prevention of its dissemination [48]. NGAL production from exogenously administrated mesenchymal stem cells can also assist in bacterial clearance from the lungs [49]. Thus, NGAL may play a protective role against lung infections from siderophore-producing bacteria. In addition, exogenous NGAL was shown to promote clearance of *Staphylococcus aureus* and dampen lung inflammation [50].

One in vitro study has suggested that NGAL may also participate in host defense against *Chlamydia pneumoniae*. Higher numbers of *C. pneumoniae*, a pathogen responsible for a large portion of community-acquired pneumonia (CAP), have been observed in cultured peritoneal macrophages derived from NGAL KO mice [51].

NGAL is able to bind and sequester enterobactin, the siderophore produced by *Klebsiella pneumoniae,* a common gram-negative pathogen of the respiratory tract. However, some strains of this organism can employ additional siderophores such as yersiniabactin and salmochelin, which cannot be sequestered by NGAL within the lung tissue, thus evading its bacteriostatic effects [52]. *K. pneumoniae* strains, isolated from the respiratory tract or that exhibit carbapenemase production, are more likely to be yersiniabactin-secreting strains [53]. In an experimental model of *K. pneumoniae* pneumonia, NGAL was indispensable for the prevention of perivascular invasion and dissemination. However, infection with yersiniabactin-positive strains was associated with a greater extent of lung pathology [54].

Pseudomonas aeruginosa, another lung pathogen related to high morbidity and mortality especially in cystic fibrosis patients, secretes pyochelin and pyoverdine, siderophores that evade NGAL recognition [55]. In clinical settings, NGAL was not a biomarker for pulmonary exacerbation in cystic fibrosis even though patients displayed higher serum levels of NGAL compared with healthy controls [56].

Tuberculosis is a re-emerging infection worldwide, and knowledge of the innate defenses against *Mycobacterium tuberculosis* is of great interest. NGAL is able to bind siderophores employed by *Mycobacterium* species, such as exochelins, mycobactins and carboxymycobactins [57]. However, carboxymycobactins are a chemically heterogenous group, and NGAL has a different affinity for each member depending on the length of the fatty acid tail present [58, 59]. Some *Mycobacterium* strains have developed in vivo mechanisms to evade the bacteriostatic effect of NGAL and to obtain iron. Even though NGAL limited *M. avium* spread during the initial extracellular phase of infection in vivo, it could not contribute to bacterial clearance in the context of long-term infection. Intracellular *M. avium* in macrophages evades endocytosed NGAL present within lysosomes, but still retains access to transferrin by residing in different intracellular compartments [60]. On the other hand, exogenously administered NGAL limited the intracellular growth of *M. tuberculosis* within macrophages in vitro [61]. In an experimental model of *M. tuberculosis* pulmonary infection, during the initial phase, NGAL was secreted into the alveolar space by alveolar macrophages and epithelial cells. Increased mycobacterial growth within alveolar epithelial cells was observed in NGAL KO mice. Moreover, internalization via endocytosis of the NGAL molecule was pivotal for the inhibition of intracellular mycobacteria growth within alveolar epithelial cells, possibly due to co-localization in the same cellular compartments [62]. Recent evidence suggests an additional role for NGAL in the context of mycobacterial pulmonary infections, that of cytokine regulator. More specifically, NGAL constrains CXCL9 induction, a lymphocyte recruiting chemokine, which promotes T lymphocyte accretion and subsequent granulomatous inflammation. Also, NGAL stimulates granulocyte colony-stimulating factor (G-CSF) and keratinocyte-derived chemokine (KC) production and enhances neutrophil recruitment [63]. In clinical settings, higher levels of NGAL and the NGAL/MMP-9 complex were detected in hospitalized adult patients with CAP compared with healthy controls. Also, plasma levels of NGAL but not C-reactive protein (CRP) before initiation of antibiotic treatment correlated with the severity of CAP [64].

Peritoneal cavity

NGAL has been isolated from peritoneal exudates of patients with severe acute peritonitis, and its levels strongly correlated with leukocyte elastase and neutrophil proteinase 4 activity, suggesting its neutrophilic origin [65]. Peritoneal mesothelial cells, after stimulation by IL-1, may also provide an additional source of NGAL within the peritoneal cavity [66]. In clinical settings, NGAL can be employed to discriminate bacterial from non-bacterial causes of peritonitis in patients undergoing peritoneal dialysis [66, 67]. Also, when combined with lactic dehydrogenase measurement, the presence of NGAL can differentiate with high accuracy bacterial peritonitis in patients with new onset non-malignant ascites [68].

Urinary tract

The urinary NGAL (uNGAL) concentration correlates with urinary white blood cell count [69]. Recent evidence from a murine model demonstrated that kidney α-intercalated cells, which are located within the collecting ducts and modulate acid–base balance, can also detect the presence of uropathogenic *E. coli*, via TLR4 and actively secrete NGAL. This contributes to bacterial clearance from the urinary tract [70]. In vivo and in vitro experiments suggest that glomerular podocytes are also capable of producing NGAL following stimulation by LPS [71]. Increased levels of uNGAL have been observed in a murine model of acute pyelonephritis, with macrophages and damaged renal tubular cells identified as the source. Interestingly, elevated NGAL expression in renal tubular cells persisted even after bacterial clearance, coinciding with the development of renal scaring [72]. Mean levels of uNGAL were elevated in adult patients with upper and lower urinary tract infections (UTIs) when compared to healthy controls [73].

Due to the detrimental sequelae of untreated UTIs and its high incidence within the pediatric population, there is interest in the discovery of novel noninvasive markers for its early detection and NGAL has been proposed as a candidate marker. Higher mean uNGAL levels were observed in children with UTI. Also, the mean urinary NGAL/creatine ratio (which controls for urinary dilution effect) was increased in the UTI group. The sensitivity of these markers out-performed leukocyte esterase and the nitrite test but displayed inferior specificity [74]. Mean urinary MMP-9/NGAL complex/creatine levels were also elevated in children with UTI when compared to normal controls or asymptomatic children with contaminated urine, and they decreased after initiation of antibiotic treatment [75]. Likewise, the mean uNGAL/creatine ratio was increased in children with febrile UTI when compared to non-febrile and febrile control groups [76]. Moreover, median plasma levels of NGAL on admission were elevated in children with UTI complicated with pyelonephritis compared with controls and uncomplicated UTI, but its usefulness as a stand-alone test for diagnosing acute pyelonephritis was considered limited [77]. Contrary to the previous results, a large-scale study recruiting children with/without UTI failed to reproduce the aforementioned findings or detect a statistically significant difference regarding uNGAL or serum NGAL levels [78].

Hepatocytes

Recent evidence from murine models indicates that liver is a significant source of NGAL under a number of conditions. More specifically, following a bacterial infection, hepatocytes produce significant amounts of NGAL possibly through activation of the STAT3 pathway [13]. In addition, hepatectomy strongly induces hepatic NGAL expression [79]. Its role in liver regeneration, however, remains to be determined. Nevertheless, NGAL appears to exert a protective effect during acute liver injury, correlating with the degree of inflammation [80].

Sepsis

After systematic administration of LPS in a murine model mimicking sepsis, an increase in serum NGAL levels was observed. NGAL gene expression was induced in liver and lung macrophages, as well as in type II alveolar cells, with TLR4 having a key role in LPS-induced NGAL gene up-regulation [81, 82]. Moreover, NGAL KO mice displayed increased LPS-related toxicity, pro-inflammatory gene expression, immune cell apoptosis and oxidative stress, with the latter being linked to delayed hypoferremia [81]. In a clinical setting, septic patients diagnosed with systematic inflammatory response syndrome (SIRS) had higher plasma NGAL levels than did other patients admitted to the ICU [83]. In another study recruiting critically ill patients, NGAL levels differed significantly only when a sepsis diagnosis was based on procalcitonin (PCT) values [84]. Also, neonates with severe sepsis had elevated serum and uNGAL when compared to a control group, and its levels strongly correlated with CRP and PCT levels [85]. In addition, plasma NGAL could discriminate fairly well the presence of bacterial sepsis from other non-infectious causes of SIRS in ICU patients, outperforming both PCT and CRP [86]. It should be noted that serum NGAL levels at presentation in sepsis patients are affected by the patient's age, even after controlling for sepsis severity [87]. NGAL levels may also be useful in discriminating patients

with septic from non-septic-induced AKI or identify septic patients who subsequently develop AKI [83, 88]. It must be acknowledged, however, that in a septic patient, NGAL present in serum and urine may be of multiple cell origin. The pathophysiology of AKI in septic patients is complex and has not yet been fully elucidated. Overlapping mechanisms involved in the pathogenesis of septic-induced AKI may include tissue hypoperfusion, alterations of renal microcirculation, release of inflammatory mediators and adaptive responses of tubular cells [89]. In this context, there is a need for the development of biomarkers that can assist physicians in discriminating the dominant underlying pathophysiologic mechanism of AKI in a septic patient and guide the application of tailor-made interventions. A potential candidate marker may be NGAL, and further clinical research is warranted in this direction.

Fungal infections

The NGAL gene was shown to be highly induced in a murine model of oropharyngeal candidiasis. However, not only did this not confer any protection, but NGAL KO mice displayed a lower fungal load [90]. This may be attributed to the fact that *Candida albicans* does not produce any siderophores on its own, but has the ability to uptake bacterial siderophores [91]. Contrary to these results, NGAL did confer a protective effect in a murine model of systematic infection from *C. albicans* [20]. Recent experiments from our laboratory demonstrated that a cultured vaginal epithelial cell line was induced to secrete NGAL following co-culture with *C. albicans.* Similarly, when compared to healthy controls, women with vulvovaginal candidiasis had elevated NGAL levels in their vaginal secretions [92].

Genital tract bacterial infections

Plasma levels of NGAL and NGAL/MMP-9 complexes were shown to be elevated in women with pelvic inflammatory disease (PID) when compared to healthy controls. These values dropped significantly following a 3-day antibiotic treatment [93]. However, plasma NGAL levels in PID patients did not further increase in the presence of a tubo-ovarian abscess [94]. NGAL is present in vaginal fluid, and its concentration is reduced in women with bacterial vaginosis, a common disorder in which *Lactobacilli* are replaced by large numbers of anaerobic bacilli and facultative bacteria. Vaginal NGAL levels were strongly correlated with the vaginal L-lactic acid concentration, suggesting that vaginal *Lactobacilli* may enhance production of NGAL [92]. Studies are lacking on the possible role of NGAL in male genital tract infections such as prostatitis and epididymitis.

Infection-related preterm birth

NGAL has been shown to be constitutively present in human fetal trophoblast cells but absent from cells in the maternal decidua. Furthermore, elevated NGAL levels were observed in placental tissues from women with an intraamniotic infection. The in vitro stimulation of trophoblast cells with IL-1β or TNF-α also enhanced NGAL production [95]. Thus, it appears that fetal NGAL participates in antimicrobial immunity during gestation. There is also evidence that alterations in NGAL concentrations are characteristic of other non-infectious disturbances of pregnancy such as preeclampsia and gestational diabetes [96, 97].

Viral infections

The role of NGAL in defense against viral infections has not been clearly defined, with only a small number of studies being published. Serum NGAL was able to discriminate between viral and bacterial infections with a higher sensitivity and specificity than CRP in a sample of patients with acute infections [98]. NGAL did not have a protective effect against West Nile encephalitis even though its gene expression was induced in brain tissue [99]. Other viruses, such as rotavirus and SV40 virus, induce NGAL gene expression in human intestinal epithelial cells and murine kidney cells, respectively [100, 101]. NGAL gene up-regulation has been detected in human papillomavirus (HPV)-positive cervical lesions, as well as in HPV-infected keratinocytes [102, 103]. Human immunodeficiency virus (HIV)-infected patients display significantly decreased serum NGAL levels when compared to healthy controls, which rise after initiation of highly active antiretroviral therapy (HAART), especially in the case of good responders. These findings may be linked to the neutrophil count since a strong positive correlation existed with NGAL levels [104]. Furthermore, NGAL is a promising marker in the diagnosis of HIV-associated nephropathy, a progressive form of chronic kidney disease that is currently diagnosed by an invasive renal biopsy [105].

Bacterial resistance to NGAL

Bacteria are under intense selective pressure to overcome the effects of NGAL on reducing iron availability, and some species have developed a variety of mechanisms to evade this bacteriostatic properties. *Haemophilus influenza*

Table 2 Siderophores evading sequestration from NGAL

Siderophore	Microbe	References
Petrobactin	*Bacillus anthracis*, *Bacillus cereus*	[107]
Vulnibactin	*Vibrio vulnificus*	[108]
Pyoverdine	*Pseudomonas aeruginosa*	[55]
Aerobactin	Enterobacteriae	[14]
Yersiniabactin	*Yersinia pestis*, *Klebsiella pneumoniae*	[53]
Ferrichrome	*Aspergillus* spp., *Microsporum* spp., *Trichophyton* spp.	[14]
Rhizoferrin	*Zygomycetes* spp.	[14]
Carboxymycobactins (certain)	*Mycobacterium* spp.	[58]
Salmochelin	*Escherichia coli*, *Salmonella* spp., *Klebsiella pneumoniae*	[111]

and *Streptococcus pneumoniae* have developed alternative modes of iron acquisition that do not rely on siderophores [106]. Other bacteria secrete "stealth" siderophores that are not recognized and sequestered by NGAL. These include petrobactin of *Bacillus anthracis* and *B. cereus* [107], vulnibactin of *Vibrio vulnificus* [108], pyoverdine of *P. aeruginosa* [55], certain carboxymycobactins [58], aerobactin of *Enterobacteria* [14] and yersiniabactin of *Yersinia pestis* and *K. pneumoniae* [53]. Fungi such as *Aspergillus, Microsporum* and *Trichofyton* secrete a hydroxamate siderophore known as ferrichrome, and *Zygomycetes* employs a citric acid-based polycarboxylate siderophore, rhizoferrin, that cannot be bound by NGAL [14]. NGAL-resistant bacterial siderophores are listed in Table 2.

A second bacterial resistance mechanism to NGAL involves the addition of sugars to the siderophore molecule, which makes it bulkier and clashes sterically with the critical residues of the binding pocket of NGAL, thus rendering impossible its recognition and sequestration [109, 110]. In addition, glycosylation can enhance the aqueous solubility of some siderophores, such as enterobactin, boosting its biological activity [109]. C-glycosylated enterobactin, known as salmochelin, has been isolated from enteric *E. coli*, *Salmonella* spp. and *K. pneumoniae* [111].

Conclusions and future directions

NGAL is constituently present within neutrophils as well as in many other tissues and is a contributing component of innate immunity, mainly by binding bacterial siderophores and depriving bacteria of iron. The observation that NGAL production increases in response to a variety of stimuli limits its applicability as a diagnostic marker for a specific infection in clinical practice. However, in normally sterile compartments such as CSF, the peritoneal cavity or urinary tract and especially in patients without kidney pathology, detection of NGAL may be effective for differential diagnosis of a bacterial infection. Additional clinical trials are needed for the validation of this biomarker in specific pathologies and toward the elucidation of its role in genital tract infections. Also, investigation into the occurrence of NGAL gene polymorphisms that may increase susceptibility of certain individuals to infections would be of great interest. Some bacteria have developed multiple mechanisms to evade the anti-iron bacteriostatic effect of NGAL, and further research is needed to identify reagents effective against NGAL-resistant siderophores. An improved knowledge of host defenses and bacterial resistance mechanisms may aid clinicians in better understanding the pathophysiology of various infections as well as the development of novel prevention and treatment strategies.

Conflict of interest The authors report no conflict of interest.

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