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Lactoferrin in periodontology-A review

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Abstract
Lactoferrin, a multifunctional glycoprotein belonging to the transferrin family, has gained significant attention in the field of periodontology due to its promising therapeutic properties. This abstract provides an overview of the role and potential applications of lactoferrin in periodontal health and disease management. Lactoferrin's ability to bind iron and modulate the host immune response plays a crucial role in inhibiting bacterial growth, biofilm formation, and reducing inflammation at the periodontal site. Several studies have highlighted its antimicrobial efficacy against periodontopathogens, such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans. Moreover, lactoferrin's immunomodulatory effects demonstrate its capacity to regulate inflammatory cytokines, protect gingival tissues from oxidative stress, and promote tissue repair. This abstract explores the potential use of lactoferrin as an adjunctive therapeutic agent in periodontal therapy, emphasizing the need for further research to harness its full clinical benefits in periodontal disease prevention and treatment.

Keywords: Lactoferrin, lactoferrin in periodontology

Introduction

Lactoferrin is a glycoprotein that is widely present in several biological fluids such as milk, tears, saliva, and mucus. It belongs to the transferrin family and is a multifunctional protein that plays a crucial role in the innate immune response and has several other biological activities. This article reviews the biochemistry of lactoferrin, its antimicrobial properties, and its role in periodontal disease.

Structure

Lactoferrin is a glycoprotein with a molecular weight of approximately 80 kDa. It consists of two homologous lobes, each consisting of a single polypeptide chain with 337 amino acids. Each lobe has an iron-binding site, which is responsible for its biological activity. Lactoferrin has a high affinity for iron, and its binding to iron is pH-dependent. At acidic pH, lactoferrin binds iron tightly, whereas at neutral pH, iron is released from lactoferrin. Lactoferrin has several isoforms, and the two major isoforms are lactoferrin-A and lactoferrin-B. These isoforms differ in their glycosylation patterns [1].

Lactoferrin has several antimicrobial properties that make it an important component of the innate immune system. Lactoferrin binds to bacterial cell membranes and disrupts their integrity, leading to bacterial death. Lactoferrin also chelates iron, which is essential for bacterial growth, thereby limiting bacterial proliferation. Lactoferrin has been shown to be effective against several bacterial species, including Escherichia coli, Staphylococcus aureus, Streptococcus mutans, and Candida albicans. Lactoferrin also has antiviral and antifungal properties [2].

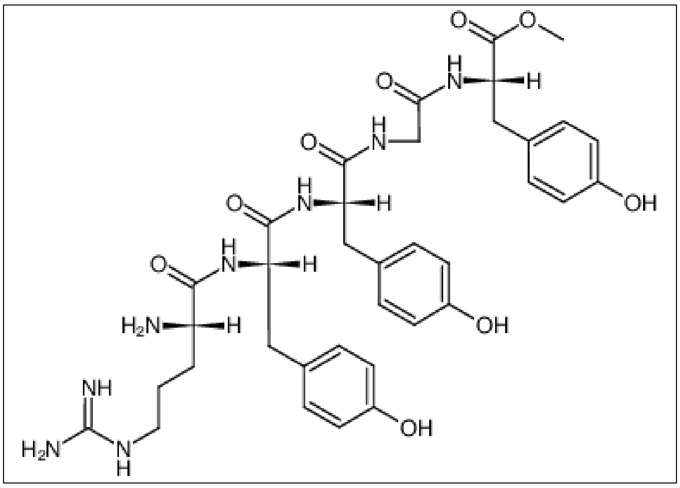

Fig 1: Lactoferrin structure

Biochemistry of Lactoferrin

Lactoferrin is an iron-binding glycoprotein that is present in several biological fluids such as milk, tears, saliva, and mucus [3]. It belongs to the transferrin family and is a multifunctional protein that plays a crucial role in the innate immune response and has several other biological activities. The biochemistry of lactoferrin is well-characterized, and it is known to be a glycoprotein with a molecular weight of approximately 80 kDa. It contains two homologous lobes, each consisting of a single polypeptide chain with 337 amino acids. The lobes are connected by a hinge region and can move independently, allowing lactoferrin to adopt different conformations. Each lobe has an iron-binding site, which is responsible for its biological activity.

The iron-binding site in each lobe of lactoferrin consists of two histidine residues, one aspartic acid residue, and one tyrosine residue. These residues form a cleft that can bind one iron ion. Lactoferrin has a high affinity for iron, with a binding constant of approximately 10^20 M^-1. The binding of iron to lactoferrin is pH-dependent. At acidic pH, lactoferrin binds iron tightly, whereas at neutral pH, iron is released from lactoferrin. This pH-dependent binding of iron allows lactoferrin to sequester iron from bacteria in acidic environments such as the stomach, preventing bacterial growth [4].

Lactoferrin has several isoforms, and the two major isoforms are lactoferrin-A and lactoferrin-B. These isoforms differ in their glycosylation patterns, with lactoferrin-B having an additional N-glycosylation site. The glycosylation of lactoferrin is important for its stability, solubility, and biological activity.

In addition to its iron-binding properties, lactoferrin has several other biological activities. It has been shown to have antimicrobial, antiviral, and antifungal properties. Lactoferrin binds to bacterial cell membranes and disrupts their integrity, leading to bacterial death. Lactoferrin also chelates iron, which is essential for bacterial growth, thereby limiting bacterial proliferation. Lactoferrin has been shown to be effective against several bacterial species, including Escherichia coli, Staphylococcus aureus, Streptococcus mutans, and Candida albicans. Lactoferrin also modulates the host immune response by stimulating the production of cytokines and chemokines that recruit immune cells to the site of infection. Lactoferrin also enhances the phagocytic activity of immune cells, leading to bacterial clearance.

Mechanism of Action

Lactoferrin is a multifunctional protein that exerts a variety of actions in the body. Here are some of its main actions with references

Antimicrobial activity

Lactoferrin has potent antimicrobial activity against a broad spectrum of microorganisms, including bacteria, viruses, and fungi. It binds to the cell membrane of pathogens and disrupts their integrity, leading to cell death. Lactoferrin also chelates iron, which is essential for bacterial growth, thereby limiting bacterial proliferation.

Immunomodulatory activity

Lactoferrin modulates the immune response by enhancing the function of immune cells, such as macrophages, natural killer cells, and T cells. It also stimulates the production of cytokines and chemokines that recruit immune cells to the site of infection.

Anti-inflammatory activity

Lactoferrin has anti-inflammatory properties and can reduce inflammation in various tissues, including the gut and the skin. It inhibits the activation of nuclear factor kappa B (NF-κB), a transcription factor that regulates the expression of pro-inflammatory cytokines.

Wound healing activity

Lactoferrin promotes wound healing by enhancing the migration and proliferation of keratinocytes and fibroblasts, two cell types involved in the wound healing process. It also stimulates angiogenesis, the formation of new blood vessels, which is essential for tissue repair.

Anti-cancer activity

Lactoferrin has been shown to have anti-cancer activity by inhibiting the growth and metastasis of cancer cells. It induces apoptosis, programmed cell death, in cancer cells and inhibits angiogenesis, the formation of new blood vessels that is necessary for tumor growth [5, 6, 7].

USES

Lactoferrin has been studied extensively for its potential uses in dentistry due to its antimicrobial and immunomodulatory properties. Here are some examples of its uses:

Oral Candidiasis

Oral candidiasis is a common fungal infection in the oral cavity. Lactoferrin has been shown to have antifungal properties against Candida albicans, a common causative agent of oral candidiasis. A study demonstrated that lactoferrin can inhibit the growth of Candida albicans and suppress the formation of biofilm [8].

Dental Caries

Dental caries are caused by acid-producing bacteria in the oral cavity. Lactoferrin has been shown to inhibit the growth of cariogenic bacteria, such as Streptococcus mutans, by chelating iron, which is essential for bacterial growth [9]. A study found that lactoferrin can also promote remineralization of enamel, which may prevent dental caries [10].

Others

People commonly use lactoferrin for low iron levels during

- pregnancy
- for preventing blood infections (sepsis) in premature infants.
- It is also used for diarrhea, common cold, and many other conditions.
- hepatitis C; Some patients with hepatitis C seem to respond to bovine lactoferrin. Doses of 1.8 or 3.6 grams/day of lactoferrin are needed

Overall, lactoferrin has shown promise as a potential therapeutic agent in dentistry due to its antimicrobial and immunomodulatory properties. Further studies are needed to fully understand its mechanisms of action and potential clinical applications.

Antimicrobial properties

Lactoferrin can inhibit the pathogen from binding to the host by binding to the lipopolysaccharide of the bacterial wall, ultimately resulting in bacterial cell lysis. Lactoferrin promotes the growth of beneficial bacteria with low iron requirements, such as Lactobacillus and Bifidobacterium [11].

Transferrin and lactoferrin are proteins that possess bacteriostatic properties by removing iron from the extracellular environment, which is essential for microorganisms' growth. Lactoferrin contributes to mucosal defense mechanisms by delaying the growth of bacteria and fungi, demonstrating antimicrobial activity against a wide range of pathogenic agents, including bacteria, yeast, fungi, protozoa, and viruses [12]. However, an excess of iron can reverse lactoferrin's inhibitory effect on microbial growth. Lactoferrin's multifunctional ability includes chelation, which inhibits microbial growth, as well as the formation of lactoferricin, a peptide with antimicrobial activity. Lactoferrin can also interfere with the colonization factors of tissues. Moreover, it has been found that lactoferrin's binding to the lipid A of LPS induces the release of LPS, leading to bactericidal activity. Lactoferrin's N-terminal region, including the 1-11 residues, possesses antibacterial activity against Streptococcus mutans through binding with bacterial DNA. Lactoferricin is several times more active than the intact protein, suggesting that lactoferrin's bactericidal activity is located in its N-terminal region [13].

In saliva

The concentration of Lf is affected by various factors, including the type of saliva samples (stimulated or unstimulated) and the age of the individual. In patients with gingivitis, chronic periodontitis, and localized juvenile periodontitis, the levels of Lf in GCF were reported to be higher than those of normal individuals. Furthermore, a study found that the levels of Lf in GCF were correlated with the severity of periodontal disease and the number of polymorphonuclear leukocytes. A decrease in Lf levels was observed in GCF and saliva after surgical periodontal treatment in chronic periodontitis, and a similar decrease was detected after oral hygiene procedures in experimental gingivitis using healthy volunteers [14]. Lf is not synthesized in healthy gingival tissues and is released from neutrophils in GCF in response to the inflammatory condition of periodontitis, serving as a host defense factor against periodontopathic bacteria and potentially indicating the presence of periodontal disease [15].

As an antioxidant

To prevent damage to healthy tissues caused by highly reactive mediators, the body employs antioxidant mechanisms. When hydrogen peroxide reacts with superoxide, it produces hydroxyl radicals (-OH-) that are extremely reactive and require iron or copper ions to catalyze the reaction. Thus, the role of lactoferrin in defending against the aggression of these reactive agents is determined by its ability to capture these ions. An imbalance in the levels of myeloperoxidase/IL-1β and peroxidase/lactoferrin glutathione can lead to tissue damage caused by reactive oxygen species (ROS) in periodontitis, which is initiated and perpetuated by pathogenic agents that affect the periodontium [16].

Lactoferrin in periodontology

As an inflammatory marker

Lactoferrin has been identified as a potential biochemical marker for periodontal disease due to its involvement in several biological processes. Several studies have been conducted since 1993 to investigate the relationship between lactoferrin levels in crevicular gingival fluid (CGF) and the number of polymorphonuclear neutrophils present in periodontal disease. Lactoferrin released by polymorphonuclear leukocytes into the CGF can be used as an indicator of periodontal inflammation, with higher levels detected in patients with juvenile periodontitis, gingivitis, and adult periodontitis in relation to inflammation severity. This makes lactoferrin quantification a useful tool for detecting the degree of periodontal inflammation. In addition, lactoferrin has been shown to have anti-invasive activity against S. mutans infecting gingival fibroblasts. The response of neutrophil granulocytes is also important in periodontal disease, and components of CGF can be used to identify or diagnose active disease and anticipate the risk of contracting it, as well as to determine its progression [17].

Anti-inflammatory activity

The milk-derived substance bovine lactoferrin (bLf) is becoming increasingly recognized as an important regulator of iron and inflammatory homeostasis, with a powerful ability to reduce inflammatory responses. This ability is attributed to bLf's capacity to bind free iron, which can be potentially toxic, and to sequester LPS, thus counteracting its biological activity [18]. Additionally, bLf can inhibit biofilm development, leading to a reduction in inflammation caused by the exopolysaccharides that form the biofilm. Since no ideal therapy currently exists for treating periodontitis, the oral administration of bLf, with its anti-inflammatory efficacy, holds promise for the development of new therapeutic approaches to treating periodontal diseases [19].

Biofilm formation inhibition

Biofilms are groups of microorganisms that are highly successful in colonizing various surfaces and are responsible for causing numerous diseases. They are communities of microorganisms that grow within a self-produced matrix of exopolysaccharides, adhering to both inert surfaces and living tissues [20]. The formation of biofilms occurs through a continuous process that can be divided into several phases:

a. conditioning,
b. adhesion,
c. extracellular matrix synthesis
d. maturation and
e. dispersion

Bacterial biofilm is the primary etiological factor for periodontal disease.

Lactoferrin has the ability to interact with microbial components and chelate ions, which makes it a potential modifier of microorganism interactions with tissue surfaces. The interference of lactoferrin in the development phases of biofilms has been studied due to its ability to suppress the initial union of S. gordonii and its coaggregation through iron abduction, resulting in the inhibition of the initial phase and development of the oral biofilm. Lactoferrin also prevents biofilm formation on bacteria that have escaped initial death and stimulates a unique type of bacterial locomotion that creates distance between daughter cells from the site of parental division. Recent studies have shown that lactoferrin reduces the number of P. gingivalis and P. intermedia in subgingival plaque of patients with chronic periodontitis. Therefore, the use of lactoferrin, including human and bovine apo and holo forms as well as lactoferricin, is proposed for the prevention and treatment of periodontal diseases, especially when used in combination with antibiotics [21, 22].

Uses in periodontology

Periodontal Disease

Several studies have investigated the role of lactoferrin in the treatment of periodontal disease. Topical application of lactoferrin has been shown to reduce clinical signs of periodontitis, including bleeding on probing, probing depth, and attachment loss [23]. Additionally, lactoferrin has been shown to inhibit the growth of periodontal pathogens such as Porphyromonas gingivalis and Prevotella intermedia.

Implant Dentistry

Implant-associated infections are a common complication in implant dentistry. Lactoferrin has been shown to prevent bacterial adhesion and biofilm formation on implant surfaces [24]. A study found that the incorporation of lactoferrin into implant coatings can significantly reduce bacterial adhesion and promote osseointegration [25].

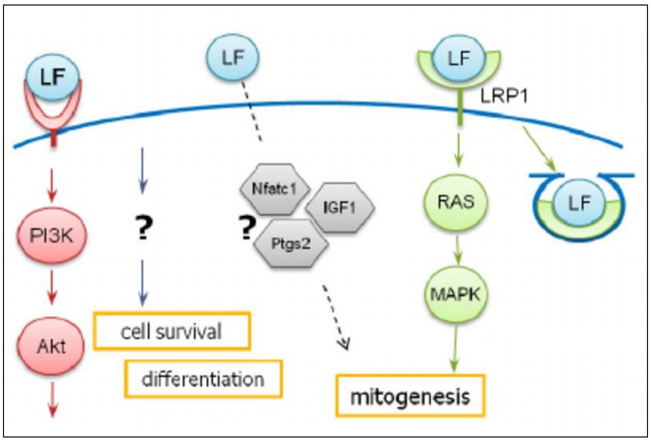

Fig 1: (Lactoferrin as an effector molecule in the skeleton, 23, 2010, 425-430, Cornish, J. & Naot, D.)

In diagnosis

Lactoferrin levels in tear fluid have been shown to decrease in dry eye diseases such as Sjögren's syndrome. A rapid, portable test utilizing microfluidic technology has been developed to enable measurement of lactoferrin levels in human tear fluid at the point-of-care with the aim of improving diagnosis of Sjögren's syndrome and other forms of dry eye disease [26].

Recent advancements

Nanotechnology

Lactotransferrin has been used in the synthesis of fluorescent gold quantum clusters, which has potential applications in nanotechnology [27].

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