Abstracts Lactoferrine

Biometals. 2018 Mar 7. doi: 10.1007/s10534-018-0092-8. [Epub ahead of print]

Physico-chemical properties influence the functions and efficacy of commercial bovine lactoferrins.

Rosa L[1], Cutone A[1,2], Lepanto MS[1], Scotti MJ[1], Conte MP[1], Paesano R[3], Valenti P[4].

Human and bovine lactoferrin (hLf and bLf) are multifunctional iron-binding glycoprotein constitutively synthesized and secreted by glandular epithelial cells and by neutrophils following induction. HLf and bLf possess very high similarity of sequence. Therefore, most of the in vitro and in vivo studies are carried out with commercial bLf (cbLf), available in large quantities and recognized by Food and Drug Administration (FDA, USA) as a safe substance. Physico-chemical heterogeneity of different cbLf preparations influences their effectiveness. CbLf iron-saturation affects thermal stability and resistance to proteolysis. Moreover, other metal ions such as Al(III), Cu(II), Mg(II), Mn(II), Zn(II) are chelated by cbLf, even if at lower affinity than Fe(III). Ca(II) is also sequestered by the carboxylate groups of sialic acid present on glycan chains of cbLf thus provoking the release of LPS, contributing to bactericidal activity. Similarly to more than 50% of eukaryotic proteins, cbLf possesses five N-glycosylation sites, also contributing to the resistance to proteolysis and, putatively, to the protection of intestinal mucosa from pathogens. CbLfs possess several functions as anti-microbial, anti-biofilm, anti-adhesive, anti-invasive and anti-inflammatory activities. They are also relevant modulators of iron and inflammatory homeostasis. However, the efficacy of cbLfs in exerting several functions can be erratic mainly depending from integrity, degree of iron and other metal ions saturation, N-glycosylation sites and chains, desialylated forms, Ca(II) sequestration, presence of contaminants and finally the ability to enter inside nucleus.

KEYWORDS:

Anaemia of inflammation; Commercial bovine lactoferrins; Iron deficiency anaemia; Lactoferrin; Lipopolysaccharide release; Metal-binding ability

Eur J Obstet Gynecol Reprod Biol. 2017 Dec;219:45-52. doi: 10.1016/j.ejogrb.2017.10.003. Epub 2017 Oct 4.

Lactoferrin or ferrous salts for iron deficiency anemia in pregnancy: A meta-analysis of randomized trials.

Abu Hashim H[1], Foda O[2], Ghayaty E[3].

Author information

Abstract

This systematic review and meta-analysis aimed to evaluate the efficacy of daily oral bovine lactoferrin versus daily oral ferrous iron preparations for treatment of iron deficiency anemia (IDA) during pregnancy. Searches were conducted on PubMed, ScienceDirect, ClinicalTrials.gov and CENTRAL databases from inception to February 2017 and the bibliographies of retrieved articles were screened. The PRISMA Statement was followed. Published English language randomized trials comparing lactoferrin with oral ferrous iron preparations in pregnant women with iron deficiency anemia were included. Quasi-randomized, non- randomized or studies including other known cause of anemia, gestational or pre-existent maternal diseases were excluded. Accordingly, 4 eligible trials (600 women) were analyzed. Primary outcome was change in hemoglobin level at 4 weeks of treatment. Secondary outcomes were; change in serum ferritin and iron, rates of gastrointestinal side effects, preterm birth, low birthweight, neonatal death and mean birthweight. Quality assessment was performed by the Cochrane risk of bias tool. Odds ratio and mean difference were used to integrate dichotomous and continuous outcomes respectively. Pooled estimates for change in hemoglobin levels at four weeks favored daily oral lactoferrin over daily oral ferrous sulphate (mean difference 0.77; 95% confidence interval [CI] 0.04-1.55; P=0.04, 4 trials, 600 women). However, after subgroup analysis (degree of anemia), no significant difference in hemoglobin levels were found between both groups in mild anemia (mean difference 0.80; 95% CI -0.21 to 1.82, 3 trials, 372 women), but a significant increase favoring lactoferrin was reported in moderate anemia (mean difference 0.68; 95% CI 0.53-0.83; P<0.00001, one trial, 228 women). Significantly less gastrointestinal side effects were reported with lactoferrin treatment. No significant differences existed with regard to other outcomes. In conclusion, for pregnant women with IDA, daily oral bovine lactoferrin is just as good as ferrous sulfate in improving hematological parameters with fewer gastrointestinal side effects. Thereby, lactoferrin should be the iron replacement agent of choice for treatment of IDA in pregnancy.

KEYWORDS: Bovine lactoferrin; Iron deficiency; Iron deficiency anemia; Lactoferrin; Pregnancy

Int J Hematol. 2017 Nov 16. doi: 10.1007/s12185-017-2366-2. [Epub ahead of print]

Iron and infection.

Ganz T[1].

- Correction to: Iron and infection. [Int J Hematol. 2017]

Abstract

Iron is an essential trace metal for nearly all infectious microorganisms, and host defense mechanisms target this dependence to deprive microbes of iron. This review highlights mechanisms that are activated during infections to restrict iron on mucosal surfaces, in plasma

and extracellular fluid, and within macrophages. Iron overload disorders, such as hereditary hemochromatosis or β-thalassemia, interfere with iron-restrictive host responses, and thereby cause increased susceptibility to infections with microbes that can exploit this vulnerability. Anemia of inflammation (formerly known as anemia of chronic diseases) is an "off-target" effect of host defense wherein inflammatory cytokines shorten erythrocyte lifespan by activating macrophages, prioritize leukocyte production in the marrow, and induce hepcidin to increase plasma transferrin saturation and the concentration of non-transferrin-bound iron.

KEYWORDS: Ferroportin; Hepcidin; Lactoferrin; Lipocalin; Nramp2

J Agric Food Chem. 2017 Dec 6;65(48):10464-10472. doi: 10.1021/acs.jafc.7b03390. Epub 2017 Nov 20.

Lactoferrin Exerts Antitumor Effects by Inhibiting Angiogenesis in a HT29 Human Colon Tumor Model.

Li HY[1], Li M[1], Luo CC[1], Wang JQ[1], Zheng N[1].

Author information

Abstract

To investigate the effect and potential mechanisms of lactoferrin on colon cancer cells and tumors, HT29 and HCT8 cells were exposed to varying concentrations of lactoferrin, and the impacts on cell proliferation, migration, and invasion were observed. Cell proliferation test showed that high dosage of lactoferrin (5-100 mg/mL) inhibited cell viability in a dose-dependent manner, with the 50% concentration of inhibition at 81.3 ± 16.7 mg/mL and 101 ± 23.8 mg/mL for HT29 and HCT8 cells, respectively. Interestingly, migration and invasion of the cells were inhibited dramatically by 20 mg/mL lactoferrin, consistent with the significant down regulation of VEGFR2, VEGFA, pPI3K, pAkt, and pErk1/2 proteins. HT29 was chosen as the sensitive cell line to construct a tumor-bearing nude mice model. Notably, HT29 tumor weight was greatly reduced in both the lactoferrin group (26.5 ± 6.7 mg) and the lactoferrin/5-Fu group (14.5 ± 5.1 mg), compared with the control one (39.3 ± 6.5 mg), indicating that lactoferrin functioned as a tumor growth inhibitor. Considering lactoferrin also reduced the growth of blood vessels and the degree of malignancy, we concluded that HT29 tumors were effectively suppressed by lactoferrin, which might be achieved by regulation of phosphorylation from various kinases and activation of the VEGFR2-PI3K/Akt-Erk1/2 pathway.

KEYWORDS: HCT8 cell; HT29 cell; angiogenesis; lactoferrin; tumor-bearing model

J Pediatr. 2017 Nov 30. pii: S0022-3476(17)31334-3. doi: 10.1016/j.jpeds.2017.09.080. [Epub ahead of print]

Exposure to Gastric Acid Inhibitors Increases the Risk of Infection in Preterm Very Low Birth Weight Infants but Concomitant Administration of Lactoferrin Counteracts This Effect.

Manzoni P[1], García Sánchez R[2], Meyer M[3], Stolfi I[4], Pugni L[5], Messner H[6], Cattani S[7], Betta PM[8], Memo L[9], Decembrino L[10], Bollani L[10], Rinaldi M[11], Fioretti M[12], Quercia M[13], Maule M[14], Tavella E[12], Mussa A[12], Tzialla C[10], Laforgia N[13], Mosca F[5], Magaldi R[11], Mostert M[15], Farina D[12]; Italian Task Force for the Study, and Prevention of Neonatal Fungal Infections and the Italian Society of Neonatology.

OBJECTIVE:

To investigate whether exposure to inhibitors of gastric acidity, such as H2 blockers or proton pump inhibitors, can independently increase the risk of infections in very low birth weight (VLBW) preterm infants in the neonatal intensive care unit.

STUDY DESIGN:

This is a secondary analysis of prospectively collected data from a multicenter, randomized controlled trial of bovine lactoferrin (BLF) supplementation (with or without the probiotic Lactobacillus rhamnosus GG) vs placebo in prevention of late-onset sepsis (LOS) and necrotizing enterocolitis (NEC) in preterm infants. Inhibitors of gastric acidity were used at the recommended dosages/schedules based on the clinical judgment of attending physicians. The distribution of days of inhibitors of gastric acidity exposure between infants with and without LOS/NEC was assessed. The mutually adjusted effects of birth weight, gestational age, duration of inhibitors of gastric acidity treatment, and exposure to BLF were controlled through multivariable logistic regression. Interaction between inhibitors of gastric acidity and BLF was tested; the effects of any day of inhibitors of gastric acidity exposure were then computed for BLF-treated vs -untreated infants.

RESULTS:

Two hundred thirty-five of 743 infants underwent treatment with inhibitors of gastric acidity, and 86 LOS episodes occurred. After multivariate analysis, exposure to inhibitors of gastric acidity remained significantly and independently associated with LOS (OR, 1.03; 95% CI, 1.008-1.067; P = .01); each day of inhibitors of gastric acidity exposure conferred an additional 3.7% odds of developing LOS. Risk was significant for Gram-negative (P < .001) and fungal (P = .001) pathogens, but not for Gram-positive pathogens (P = .97). On the test for interaction, 1 additional day of exposure to inhibitors of gastric acidity conferred an additional 7.7% risk for LOS (P = .003) in BLF-untreated infants, compared with 1.2% (P = .58) in BLF-treated infants.

CONCLUSION:

Exposure to inhibitors of gastric acidity is significantly associated with the occurrence of LOS in preterm VLBW infants. Concomitant administration of BLF counteracts this selective disadvantage.

Crit Rev Food Sci Nutr. 2017 Sep 21:1-17. doi: 10.1080/10408398.2017.1381583. [Epub ahead of print]

Lactoferrin: Structure, function, denaturation and digestion.

Wang B[1], Timilsena YP[1,2], Blanch E[1], Adhikari B[1,2].

Lactoferrin (LF) is a multifunctional protein occurring in many biological secretions including milk. It possesses iron binding/transferring, antibacterial, antiviral, antifungal, anti-inflammatory and anti-carcinogenic properties. These functional properties intimately depend on the structural integrity of LF especially its higher order conformation. LF is primarily extracted from bovine milk and it is subsequently added into many commercial products such as nutritional supplements, infant formula, cosmetics and toothpaste. LF is sensitive to denaturation induced by temperature and other physicochemical stresses. Hence, the extraction, powder formation processes of LF and processing parameters of LF-containing products have to be optimized to minimise its undesired denaturation. This review documents the advances made on structure-function relationships and discusses the effectiveness of methods used to preserve the structure of LF during thermal processing. Oral delivery, as the most convenient way for administering LF, is also discussed focusing on digestion of LF in oral, gastric and intestinal stages. The effectiveness of methods used to deliver LF to intestinal digestion stage in structurally intact form is also compared. Altogether, this work comprehensively reviews the fate of LF during thermal processing and digestion, and suggests suitable means to preserve its structural integrity and functional properties. Scope of review The manuscript aims at providing a comprehensive review of the latest publications on four aspects of LF: structural features, functional properties, nature and extent of denaturation and gastrointestinal digestion. It also analyses how these publications benefit food and pharmaceutical industries.

KEYWORDS: Denaturation; Digestion and Application; Drying; Function; Lactoferrin; Structure

J Gen Virol. 2017 Jul;98(7):1749-1754. doi: 10.1099/jgv.0.000849. Epub 2017 Jul 12.

Bovine lactoferrin activity against Chikungunya and Zika viruses.

Carvalho CAM[1], Casseb SMM[1], Gonçalves RB[2], Silva EVP[1], Gomes AMO[3], Vasconcelos PFC[1].

Chikungunya (CHIKV) and Zika (ZIKV) viruses are arboviruses which have recently broken their sylvatic isolation and gone on to spread rampantly among humans in some urban areas of the world, especially in Latin America. Given the lack of effective interventions against such viruses, the aim of this work was to evaluate the antiviral potential of bovine lactoferrin (bLf) in their

infections. Through viability, plaque, immunofluorescence and nucleic acid quantification assays, our data show that bLf exerts a dose-dependent strong inhibitory effect on the infection of Vero cells by the aforementioned arboviruses, reducing their infection efficiency by up to nearly 80 %, with no expressive cytotoxicity, and that such antiviral activity occurs at the levels of input and output of virus particles. These findings reveal that bLf antimicrobial properties are extendable to CHIKV and ZIKV, underlining a generic inhibition mechanism that can be explored to develop a potential strategy against their infections.

Ann N Y Acad Sci. 2017 Oct;1405(1):177-188. doi: 10.1111/nyas.13405. Epub 2017 Jun 14.

Lactoferrin protects against intestinal inflammation and bacteria-induced barrier dysfunction in vitro.

Hering NA[1], Luettig J[2], Krug SM[2], Wiegand S[2], Gross G[3], van Tol EA[3], Schulzke JD[2], Rosenthal R[2].

The iron-binding glycoprotein lactoferrin (LF) is naturally present in human breast milk. Several studies suggest that LF contributes to infant health and development owing to a variety of protective effects, including antimicrobial and anti-inflammatory features. Therefore, we aimed to elucidate its protective properties on intestinal epithelial barrier dysfunction induced by infection or inflammation using the human epithelial cell culture models HT-29/B6 and T84. During barrier perturbation induced by the proinflammatory cytokine tumor necrosis factor α (TNF-α), bovine LF restored tight junction (TJ) morphometry and inhibited TNF-α-induced epithelial apoptosis. This resulted in an attenuation of the TNF-α-induced decrease in transepithelial resistance (TER) and increases in permeability of fluorescein and FITC-dextran (4 kDa) and was as effective as the apoptosis inhibitor Q-VD-Oph. The enteropathogenic bacterium Yersinia enterocolitica is a frequent cause of diarrhea in early childhood. This involves focal changes in TJ protein expression and localization. LF diminished the Y. enterocolitica-induced drop in TER in the present in vitro model, which was paralleled by an inhibition of the Yersinia-induced reduction of claudin-8 expression via c-Jun kinase signaling. In conclusion, LF exerts protective effects against inflammation- or infection-induced barrier dysfunction in human intestinal cell lines, supporting its relevance for healthy infant development.
KEYWORDS: apoptosis; barrier dysfunction; lactoferrin; tight junction

Pathog Dis. 2017 Jul 31;75(5). doi: 10.1093/femspd/ftx054.

Lactobacilli-lactoferrin interplay in Chlamydia trachomatis infection.

Sessa R[1], Di Pietro M[1], Filardo S[1], Bressan A[1], Mastromarino P[1], Biasucci AV[1], Rosa L[1], Cutone A[1], Berlutti F[1], Paesano R[2], Valenti P[1].

In the cervicovaginal microenvironment, lactobacilli are known to protect against genital infections and, amongst the host defence compounds, lactoferrin has recently acquired importance for its anti-microbial and anti-inflammatory properties. An abnormal genital microenvironment facilitates the acquisition of pathogens like Chlamydia trachomatis, the leading cause of bacterial sexually transmitted infections worldwide. The aim of our study is to investigate the effects of Lactobacillus crispatus, Lactobacillus brevis and bovine lactoferrinon chlamydial infection, in order to shed light on the complex interplay between host defence mechanisms and C. trachomatis. We have also evaluated the effect of these defence factors to modulate the chlamydia-mediated inflammatory state. To this purpose, we have determined the infectivity and progeny production of C. trachomatis as well as interleukin-8 and interleukin-6 synthesis. The main result of our study is that the combination of L. brevis and bovine lactoferrin is the most effective in inhibiting the early phases (adhesion and invasion) of C. trachomatis infection of cervical epithelial cells and in decreasing the levels of both cytokines. In conclusion, the interaction between L. brevis and lactoferrin seems to play a role in the protection against C. trachomatis, reducing the infection and regulating the immunomodulatory activity, thus decreasing the risk of severe complications.

KEYWORDS: Chlamydia trachomatis; Lactobacillus spp.; cervicovaginal microenvironment; genital infection; inflammatory cytokines; lactoferrin

Eur J Clin Microbiol Infect Dis. 2017 Oct;36(10):1739-1748. doi: 10.1007/s10096-017-2987-7. Epub 2017 May 3.

Synergistic activity of synthetic N-terminal peptide of human lactoferrin in combination with various antibiotics against carbapenem-resistant Klebsiella pneumoniae strains.

Morici P[1,2], Florio W[1], Rizzato C[1], Ghelardi E[1], Tavanti A[3], Rossolini GM[4,5,6,7], Lupetti A[8].

The spread of multi-drug resistant (MDR) Klebsiella pneumoniae strains producing carbapenemases points to a pressing need for new antibacterial agents. To this end, the in-vitro antibacterial activity of a synthetic N-terminal peptide of human lactoferrin, further referred to as hLF1-11, was evaluated against K. pneumoniae strains harboring different carbapenemase genes (i.e. OXA-48, KPC-2, KPC-3, VIM-1), with different susceptibility to colistin and other antibiotics, alone or in combination with conventional antibiotics (gentamicin, tigecycline, rifampicin, clindamycin, and clarithromycin). An antimicrobial peptide susceptibility assay was used to assess the bactericidal activity of hLF1-11 against the different K. pneumoniae strains

tested. The synergistic activity was evaluated by a checkerboard titration method, and the fractional inhibitory concentration (FIC) index was calculated for the various combinations. hLF1-11 was more efficient in killing a K. pneumoniae strain susceptible to most antimicrobials (including colistin) than a colistin-susceptible strain and a colistin-resistant MDR K. pneumoniae strain. In addition, hLF1-11 exhibited a synergistic effect with the tested antibiotics against MDR K. pneumoniae strains. The results of this study indicate that resistance to hLF1-11 and colistin are not strictly associated, and suggest an hLF1-11-induced sensitizing effect of K. pneumoniae to antibiotics, especially to hydrophobic antibiotics, which are normally not effective on Gram-negative bacteria. Altogether, these data indicate that hLF1-11 in combination with antibiotics is a promising candidate to treat infections caused by MDR-K. pneumoniae strains.

KEYWORDS: Antimicrobial Peptide; Clarithromycin; Colistin; Fractional Inhibitory Concentration; Tigecycline

Int J Dermatol. 2017 Jun;56(6):686-690. doi: 10.1111/ijd.13607. Epub 2017 Mar 30.

A randomized, double-blind, placebo-controlled trial to determine the efficacy and safety of lactoferrin with vitamin E and zinc as an oral therapy for mild to moderate acne vulgaris.

Chan H[1], Chan G[1], Santos J[2], Dee K[2], Co JK[2].

Lactoferrin is an iron-binding milk-derived protein that has shown antibacterial and anti-inflammatory effects in vitro and in vivo. The objective of this study was to determine the efficacy and safety of lactoferrin, combined with vitamin E and zinc, for mild to moderate acne vulgaris. In this randomized, double-blind, placebo-controlled trial, 168 subjects aged 13-40 years old were randomly assigned to take either a capsule formulation containing lactoferrin with vitamin E and zinc or placebo twice a day for 3 months. The primary outcome measure was a reduction in the number of acne lesions compared to placebo. A total of 164 subjects completed the study per protocol. The lactoferrin group (n = 82) showed a significant median percent reduction in total lesions as early as 2 weeks (14.5%, P = 0.0120), with the maximum reduction occurring at week 10 (28.5%, P < 0.0001) compared to placebo group (n = 82). Maximum reduction in comedones (32.5%, P < 0.0001) and inflammatory lesions (44%, P < 0.0001) was also seen at week 10 compared to placebo. Sebum scores were improved by week 12. No adverse events were observed during the trial. A twice daily regimen of lactoferrin with vitamin E and zinc significantly reduced acne lesions in people with mild to moderate acne vulgaris.

Biometals. 2017 Apr;30(2):237-248. doi: 10.1007/s10534-017-9999-8. Epub 2017 Feb 9.

Prebiotic effects of bovine lactoferrin on specific probiotic bacteria.

Chen PW[1], Liu ZS[2], Kuo TC[2], Hsieh MC[2], Li ZW[2].

Bovine lactoferrin (bLf) is a natural iron-binding protein and it has been suggested to be a prebiotic agent, but this finding remains inconclusive. This study explores the prebiotic potential of bLf in 14 probiotics. Initially, bLf (1-32 mg/mL) treatment showed occasional and slight prebiotic activity in several probiotics only during the late experimental period (48, 78 h) at 37 °C. We subsequently supposed that bLf exerts stronger prebiotic effects when probiotic growth has been temperately retarded. Therefore, we incubated the probiotics at different temperatures, namely 37 °C, 28 °C, room temperature (approximately 22-24 °C), and 22 °C, to retard or inhibit their growth. As expected, bLf showed more favorable prebiotic activity in several probiotics when their growth was partially retarded at room temperature. Furthermore, at 22 °C, the growth of Bifidobacterium breve, Lactobacillus coryniformis, L. delbrueckii, L. acidophilus, B. angulatum, B. catenulatum, and L. paraplantarum were completely blocked. Notably, these probiotics started regrowing in the presence of bLf (1-32 mg/mL) in a significant and dose-dependent manner. Accordingly, bLf significantly increased the growth of Pediococcus pentosaceus, L. rhamnosus, and L. paracasei (BCRC 17483; a locally isolated strain) when their growth was retarded by incubation at 22 °C. In conclusion, bLf showed inconsistent prebiotic activity in the 14 probiotics at 37 °C, but revealed strong prebiotic activity in 10 probiotic strains at 22 °C. Therefore, this study enables determining additional roles of Lf in probiotic strains, which can facilitate developing novel combinational approaches by simultaneously using Lf and specific probiotics.
KEYWORDS: Bifidobacterium; Lactic acid bacterium; Lactoferrin; Prebiotic; Probiotic

Biochem Cell Biol. 2017 Feb;95(1):31-33. doi: 10.1139/bcb-2016-0051. Epub 2016 Aug 17.

Effects of lactoferrin in 6 patients with refractory bacterial vaginosis.

Otsuki K[1], Imai N[2].

Abstract

We previously reported that lactoferrin (LF) could be effective for preventing preterm delivery and intrauterine infections, based on data derived from mice and rabbits. Here we describe 6 women with a history of multiple pregnancy losses or preterm delivery and refractory bacterial vaginosis, who received prebiotic LF therapy and delivered an infant normally. Five of the women were pregnant and one was not at the time of this study. The Ethics Committee at Showa University Hospital and Showa University Koto Toyosu Hospital approved the therapeutic protocol. Vaginal suppositories and oral prebiotic LF were administered to patients who were refractory to

conventional treatment for vaginosis and had a history of late miscarriages and very early preterm delivery due to refractory vaginitis and chorioamnionitis. LF significantly improved the vaginal bacterial flora. Lactobacillus, which was detectable in the vaginas of all patients after one month of LF therapy, gradually became dominant. The findings from these 6 patients suggest that administering LF to humans could help prevent refractory vaginitis, cervical inflammation, and preterm delivery.

KEYWORDS: Lactobacillus; accouchement prématuré; cervical inflammation; infection intra-utérine; inflammation du col utérin; intrauterine infection; preterm delivery

Biochem Cell Biol. 2017 Feb;95(1):34-40. doi: 10.1139/bcb-2016-0049. Epub 2016 Oct 21.

Effect of bovine lactoferrin on Chlamydia trachomatis infection and inflammation.

Sessa R[1], Di Pietro M[1], Filardo S[1], Bressan A[1], Rosa L[1], Cutone A[1], Frioni A[1], Berlutti F[1], Paesano R[2], Valenti P[1].

Chlamydia trachomatis is an obligate, intracellular pathogen responsible for the most common sexually transmitted bacterial disease worldwide, causing acute and chronic infections. The acute infection is susceptible to antibiotics, whereas the chronic one needs prolonged therapies, thus increasing the risk of developing antibiotic resistance. Novel alternative therapies are needed. The intracellular development of C. trachomatis requires essential nutrients, including iron. Iron-chelating drugs inhibit C. trachomatis developmental cycle. Lactoferrin (Lf), a pleiotropic iron binding glycoprotein, could be a promising candidate against C. trachomatis infection. Similarly to the efficacy against other intracellular pathogens, bovine Lf (bLf) could both interfere with C. trachomatis entry into epithelial cells and exert an anti-inflammatory activity. In vitro and in vivo effects of bLf against C. trachomatis infectious and inflammatory process has been investigated. BLf inhibits C. trachomatis entry into host cells when incubated with cell monolayers before or at the moment of the infection and down-regulates IL-6/IL-8 synthesized by infected cells. Six out of 7 pregnant women asymptomatically infected by C. trachomatis, after 30 days of bLf intravaginal administration, were negative for C. trachomatis and showed a decrease of cervical IL-6 levels. This is the first time that the bLf protective effect against C. trachomatis infection has been demonstrated.

KEYWORDS: Chlamydia trachomatis; IL-6; bovine lactoferrin; infection; inflammation; lactoferrine bovine

Biochem Cell Biol. 2017 Feb;95(1):22-30. doi: 10.1139/bcb-2016-0066. Epub 2016 Oct 26.

Lactoferrin and prematurity: a promising milk protein?

Ochoa TJ[1,2], Sizonenko SV[3].

Lactoferrin (Lf) is the major whey protein in milk, with multiple beneficial health effects including direct antimicrobial activities, anti-inflammatory effects, and iron homeostasis. Oral Lf supplementation in human preterm infants has been shown to reduce the incidence of sepsis and necrotizing enterocolitis. In preclinical models of antenatal stress and perinatal brain injury, bovine Lf protected the developing brain from neuronal loss, improved connectivity, increased neurotrophic factors, and decreased inflammation. It also supported brain development and cognition. Further, Lf can prevent preterm delivery by reducing proinflammatory factors and inhibiting premature cervix maturation. We review here the latest research on Lf in the field of neonatology.
KEYWORDS: brain; cerveau; infection; lactoferrin; lactoferrine; prematurity; prématurité

Molecules. 2015 May 26;20(6):9703-31. doi: 10.3390/molecules20069703.

Multifunctional iron bound lactoferrin and nanomedicinal approaches to enhance its bioactive functions.

Kanwar JR[1], Roy K[2], Patel Y[3], Zhou SF[4], Singh MR[5], Singh D[6], Nasir M[7], Sehgal R[8], Sehgal A[9], Singh RS[10], Garg S[11], Kanwar RK[12].

Lactoferrin (Lf), an iron-binding protein from the transferrin family has been reported to have numerous functions. Even though Lf was first isolated from milk, it is also found in most exocrine secretions and in the secondary granules of neutrophils. Antimicrobial and anti-inflammatory activity reports on lactoferrin identified its significance in host defense against infection and extreme inflammation. Anticarcinogenic reports on lactoferrin make this protein even more valuable. This review is focused on the structural configuration of iron-containing and iron-free forms of lactoferrin obtained from different sources such as goat, camel and bovine. Apart for emphasizing on the specific beneficial properties of lactoferrin from each of these sources, the general antimicrobial, immunomodulatory and anticancer activities of lactoferrin are discussed here. Implementation of nanomedicinial strategies that enhance the bioactive function of lactoferrin are also discussed, along with information on lactoferrin in clinical trials.
KEYWORDS: bovine; camel; cancer; immunity; lactoferrin; nanoparticles

Biochimie et biologie cellulaire. 2012, 90(3): 233-244, 10.1139/o2012-016

Lactoferrin, a bird’s eye view

Hans J. Vogel Biochemistry Research Group, Department of Biological Sciences, University of Calgary, Calgary, AB T2N 1N4, Canada.

La lactoferrine est une protéine de liaison du fer abondante dans le lait. Cette glycoprotéine bilobée de 80 kDa se retrouve aussi dans plusieurs autres liquides biologiques sécrétés ainsi que dans les granules secondaires des neutrophiles. Les fortes propriétés de liaison du fer de la lactoferrine peuvent créer une déficience locale en fer, constituant ainsi un facteur de défense de l'hôte important en empêchant les bactéries de croître et de former des biofilms. En plus de son activité antibactérienne, la lactoferrine est connue maintenant pour posséder de nombreuses autres propriétés bénéfiques. Elle exerce des activités antivirales, antifongiques et même quelques activités anticancéreuses directes. Elle peut aussi promouvoir la cicatrisation et la croissance osseuse, ou elle peut agir comme transporteur de fer. En outre, la lactoferrine montre une activité « alarmine » semblable à celle des cytokines et elle active le système immunitaire. Parallèlement, elle peut lier une endotoxine (lipopolysaccharide) et ce faisant, elle module l'activité de la réponse immune de l'hôte. La majorité de ces activités biologiques fascinantes reposent sur la région N-terminale de la protéine chargée positivement. Fait intéressant, plusieurs peptides, qui conservent plusieurs des activités bénéfiques, peuvent être libérés de cette région de la lactoferrine. Une isoforme de la protéine humaine, connue sous le nom de delta-lactoferrine, est exprimée à l'intérieur de plusieurs cellules où elle agit comme facteur de transcription. La lactoferrine purifiée du lait humain et celle du bovin ont des propriétés très similaires mais pas tout à fait identiques. Les récepteurs de lactoferrine ont été identifiés à la surface de différentes cellules et certains d'entre eux peuvent lier tant la lactoferrine humaine que la lactoferrine bovine. Compte tenu des effets bénéfiques considérables de la lactoferrine pour la santé humaine, l'utilisation de la lactoferrine bovine ou humaine comme nutraceutique ou comme protéine thérapeutique a suscité un grand intérêt. Lorsque la lactoferrine est utilisée comme « médicament biologique », elle semble active oralement contrairement aux autres protéines thérapeutiques.

MOTS-CLÉS : ANTIMICROBIEN, ANTICANCÉREUX, ENDOTOXINE, PROTÉINE DE LIAISON DU FER,IMMUNOMODULATEUR, FACTEUR DE TRANSCRIPTION

Lactoferrin, a key molecule in immune and inflammatory processes[1]

Dominique Legrand

UMR 8576 CNRS / Université des Sciences et Technologies de Lille, Unité de Glycobiologie Structurale et Fonctionnelle, IFR 147, F-59650 Villeneuve d'Ascq, France.

E-mail for correspondence: dominique.legrand@univ-lille1.fr.

Publié sur le Web 2 décembre 2011.

Reçu juillet 27, 2011. Accepté septembre 12, 2011.

[1]This article is part of Special Issue entitled Lactoferrin and has undergone the Journal's usual peer review process.

Biochimie et biologie cellulaire, 2012, 90(3): 252-268, 10.1139/o11-056

RÉSUMÉ

La lactoferrine (Lf) appartient à la famille des molécules antimicrobiennes constituant la principale ligne de défense des invertébrés. Chez l'Homme, leurs rôles dépassent largement les propriétés antimicrobiennes. En effet, la Lf est impliquée dans les immunités innée et acquise où ses effets modulateurs procurent à l'hôte une protection contre les microbes et les conséquences néfastes de l'inflammation. De tels effets ont été observés lors d'expérimentations utilisant la Lf dans l'alimentation, mais où les mécanismes d'action n'ont pas toujours pu être expliqués. Des effets sur les immunités mucosale et systémique ont en effet souvent été détectés, rendant les rôles de la Lf difficiles à préciser. Il est désormais admis que les propriétés immunomodulatrices de la Lf sont dues à sa capacité d'interaction avec de nombreuses cibles moléculaires et cellulaires. A l'échelle cellulaire, la Lf module la migration, la maturation et les fonctions des cellules immunitaires. A l'échelle moléculaire, les propriétés modulatrices de la Lf sont dues à sa capacité à fixer le fer, mais aussi et surtout à ses interactions avec de nombreuses cibles, solubles ou exprimées à la surface des cellules. Cette revue fait le point de nos connaissances sur les mécanismes pouvant expliquer les propriétés régulatrices de la Lf dans les processus immunitaires et inflammatoires.

Mots-clés : lactoferrine, immunité, inflammation, protéine du lait

BioMetals
June 2010, Volume 23, Issue 3, pp 589-592 - First online: 16 February 2010

Evaluation of the cytoprotective effects of bovine lactoferrin against intestinal toxins using cellular model systems

Hong Tian, Ian S. Maddox, Lynnette R. Ferguson, Quan Shu

Lactoferrin is an iron-binding glycoprotein that exhibits a range of health benefits including immune regulation and disease prevention derived from its structural properties. The present study employed immune cell models and a colon epithelial cell model to investigate the protective effects of bovine lactoferrin (BLf) on both immune cells and colon epithelium cells. BLf caused significant reduction of faecal genotoxin-induced DNA damage in HT29 cells, and down-regulation of lipopolysaccharide (LPS)-induced macrophage cell stress and endotoxic response, in an infection status.

Am J Gastroenterol. 2007 May;102(5):951-6. Epub 2007 Feb 21.

Helicobacter pylori eradication: a randomized prospective study of triple therapy versus triple therapy plus lactoferrin and probiotics.

de Bortoli N[1], Leonardi G, Ciancia E, Merlo A, Bellini M, Costa F, Mumolo MG, Ricchiuti A, Cristiani F, Santi S, Rossi M, Marchi S.

Abstract

OBJECTIVES:

Helicobacter pylori is causally associated with gastritis and peptic ulcer diseases. Recent data (meta-analysis) have demonstrated that triple therapy with amoxicillin, clarithromycin, and a

proton pump inhibitor has an eradication rate of only 74-76% and new therapeutic protocols may be necessary. The aim of this study was to examine whether adding bovine lactoferrin (bLf) and probiotics (Pbs) to the standard triple therapy for H. pylori infection could improve the eradication rate and reduce side effects.

METHODS:

H. pylori infection was diagnosed in 206 patients: in 107 based on an upper endoscopy exam and a rapid urease test, and in 99 by means of the H. pylori stool antigen-test and the C(13) urea breath test (C(13) UBT). The patients were randomized into two groups: 101 patients (group A) underwent standard triple eradication therapy (esomeprazole, clarithromycin, amoxicillin), while 105 patients (group B) underwent a modified eradication therapy (standard triple eradication therapy plus bLf and Pb). Successful eradication therapy was defined as a negative C(13) UBT 8 wk after completion of the treatment. Results were evaluated by intention-to-treat (ITT) and per-protocol (PP) analysis. Data were evaluated and considered positive when $P<0.05$.

RESULTS:

At the end of the study 175/206 patients showed negative C(13) UBT results. According to intention-to-treat analysis, the infection was eradicated in 73/101 patients from Group A and in 93/105 from Group B. PP analysis showed 73/96 patients from Group A and 93/101 from Group B to have been successfully treated. More patients from group A than from group B reported side effects from their treatment ($P<0.05$).

CONCLUSIONS:

The results of our study suggest that the addition of bLf and Pbs could improve the standard eradication therapy for H. pylori infection--bLf serving to increase the eradication rate and Pbs to reduce the side effects of antibiotic therapy.

Comment in

- A quintuple therapy for H. pylori eradication. [Am J Gastroenterol. 2007]