www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2020;9(1):e090142
doi: 10.7363/090142
Received: 2020 Apr 15; accepted: 2020 Apr 17; published online: 2020 Apr 21

Editorial

Viral infections: lactoferrin, a further arrow in the quiver of prevention

Diego G. Peroni

Department of Clinical and Experimental Medicine, Section of Paediatrics, University of Pisa, Pisa, Italy

"There is no finer investment for any community than putting milk into babies"
Winston Churchill

Keywords

Child, lactoferrin, colostrum, human milk, supplementation, premature, viral infections.

Corresponding author

Prof. Diego Peroni, UO di Pediatria, Ospedale Santa Chiara, Edificio 1, Via Roma 67, 56126, Pisa, Italy; e-mail: diego.peroni@unipi.it.

How to cite

Peroni DG. Viral infections: lactoferrin, a further arrow in the quiver of prevention. J Pediatr Neonat Individual Med. 2020;9(1):e090142. doi: 10.7363/090142.

Lactoferrin (LF) is the major serum protein in mammalian milk; it was isolated in 1960 in both human and cow's milk. It is a glycoprotein of about 690 amino acid residues, 80 kDa, which belongs to the group of transferrin, capable of chelating 2 Fe (III) atoms per molecule, with a high affinity. Many biological functions have been recognized to LF, including those of binding and releasing iron, but also of acting as a powerful component of the innate immune system by inhibiting the growth of many pathogens [1, 2]. LF has a highly conserved structure between species, therefore, it is very similar by extraction, with a high amino acid homology between different mammals, such as humans and cattle (homology equal to 77%). Both isoforms (human and bovine) share a peptide termination, called lactoferricin, which is the major responsible for the antimicrobial action [1]. Noteworthy, LF is produced and secreted by glandular epithelial cells and neutrophils, with a peak concentration in colostrum (7-8 mg/mL) and then at lower levels in mature milk (1.5-4 mg/mL) and also in exocrine secretions (saliva 0.008, joint fluid 0.001, vaginal secretion 0.008 mg/mL). In areas of infection/inflammation it is well concentrated, for the high concentration of neutrophils that produce and secrete the molecule.

For several years the antibacterial activity of LF has been known through both direct and indirect mechanisms, assuming also an immunomodulatory role. Its antimicrobial action has been proven against bacteria, fungi, viruses and parasites [3]. Its antibacterial action is mainly due to its ability to sequester the iron that bacteria need to grow and develop. A well-known group of Italian researchers have investigated the protective effects of bovine origin LF (bLF) on the prevention of sepsis in high-risk preterm infants [3, 4]. In premature babies born with very low birth weight (< 1,500 grams at birth), the administration in three different arms of bLF 100 mg/day, bLF 100 mg/day + a probiotic (*Lactobacillus GG*) or placebo was carried out for the first 30-45 days of life. The incidence of late-onset sepsis was significantly lower in the two intervention groups than in those who received the placebo, with a lower incidence of both bacterial and fungal infections. There is also a review of the *Cochrane* on this topic which shows that from the studies available on a large number of premature babies there is evidence, albeit of low quality, that supplementation with bLF with or without probiotics is able to decrease the incidence of late sepsis or necrotizing enterocolitis (NEC) without having adverse side effects [5].

However, the most intriguing demonstration of efficacy is related to effects on a wide spectrum of RNA and DNA viruses, both in the LF-free form and linked to iron. bLF appears to have equal or almost greater antiviral power than human origin LF (hLF). Both bLF and hLF have been shown to prevent infection *in vitro* in a dose-dependent mode, preventing by example the synthesis of adenovirus antigens in the first stage of infection, if LF was added to cell cultures before the viral attack, even by interfering with the primary receptors present at the cellular level. In particular, between the 2 conformal lobes of bLF (C- and N-), the fraction C- is the one that completely blocks the infection of all the major subtypes including H_1N_1 and H_3N_2. This fraction has been shown to inhibit viral hemagglutination and infection even if present (*in vitro*) at dosages of fentomoles [1].

Antiviral activity, therefore, takes place particularly at the moment of the attack by the virus on the host cell, since it prevents the virus from anchoring and then entering the host cell. Viruses use common molecules present on the cell membrane. These molecules, like heparan sulfate proteoglycans (HSPGs), make up the first anchoring site on the cell surface in the first phases of the infection. The virus then accumulates on the cell surface and penetrates the cell through highly complex mechanisms that provide for anchoring on non-specific sites and subsequent attachment to high-specific receptors, that allow the virus to entry into the cell. Among these virus-specific receptors, the receptor called angiotensin-converting enzyme 2 (ACE2), a metallopeptidase that is able to hook the terminals of the virus and facilitate the entry into the cell, should be noted. However, the HSPG molecules, that function as primary binding sites, probably further facilitate the viral concentration on the cell surface, as well as access to the more specific receptors, such as ACE2.

In vitro evidence shows that LF is able to prevent viral infection with an effect that is dose-dependent, precisely by acting through an interaction with HSPGs [6]. In fact, the elegant *in vitro* study by Lang and colleagues clearly shows that LF, binding to HPSGs, was able to inhibit the SARS Coronavirus (SARS-CoV) cell entry. LF blocks the interaction between spike viral protein and the culture cells in an ACE2-independent fashion, not disrupting the binding of the experimental virus to the ACE2. LF-mediated inhibition of SARS-CoV infection occurred through LF competitively localizing to the virus anchoring sites provided

by HSPGs, preventing in this way the preliminary contact between the SARS-CoV and host cells and the following cell entry. The authors hypothized that this mechanism of blockage by LF was able to prevent the viral concentration on the cell surface, as well as to the specific entry receptors (ACE2) [6].

The innate response of the immunological system plays a fundamental role in inhibiting viral infections, also through the action of the LF, which turns out to be over-expressed (about 150 times) in patients with proven SARS-CoV infection compared to controls, functioning by enhancing NK cell activity and stimulating neutrophil aggregation and adhesion [7]. Coming back to prevention, in a study of limited value but performed *in vivo* using a questionnaire, the administration of LF tablets to adult women was able to decrease the incidence of the symptoms of a common viral cold and the symptoms of gastroenteritis [8]. Another *in vivo* study showed that administration of LF in association with vaccine serum immunoglobulins was again able to reduce the incidence of flu symptoms [9]. A recent review also highlights how in studies in children the administration of LF has given promising effects on viral gastrointestinal infections (from norovirus in particular) with a reduction in the severity of symptoms, duration and volume of diarrhoea even if there are no differences in the incidence of infections themselves [10].

In conclusion, LF has antimicrobial effects known for years but in the last decade further mechanisms of action have been highlighted that strengthen its rationale for use, especially in the prevention of bacterial and viral infections. Consolidated data in the premature and full-term newborns have demonstrated efficacy (less incidence of late sepsis, less NEC), but also an optimal safety profile. The real challenge concerns the potential efficacy on prevention by LF of viral infections in the infants and children, including flu or even Coronavirus infections. The LF action at the level of cell receptors leads to prevent the viral anchoring, the surface accumulation and the entry into the cell. This latter mechanism, if not stopped, would then lead to viral replication, death by apoptosis of the cell and infection. Further room for improvement can be expected by the synergy of action with other supplementations, such as vitamin D [11], that could accentuate the immunological role of LF in the prevention of viral infections. However, further clinical evidence is needed, and other population studies that give clinical strength to these evidences are necessary.

Declaration of interest

The Author declares that there is no conflict of interest.

References

1. Berlutti F, Pantanella F, Natalizi T, Frioni A, Paesano R, Polimeni A, Valenti P. Antiviral Properties of Lactoferrin – A Natural Immunity Molecule. Molecules. 2011;16:6992-7018.
2. Redwan EM, Uversky VN, El-Fakharany EM, Al-Mehdar H. Potential lactoferrin activity against pathogenic viruses. C R Biol. 2014;337:581-95.
3. Manzoni P, Rinaldi M, Cattani S, Pugni L, Romeo MG, Messner H, Stolfi I, Decembrino L, Laforgia N, Vagnarelli F, Memo L, Bordignon L, Saia OS, Maule M, Gallo E, Mostert M, Magnani C, Quercia M, Bollani L, Pedicino R, Renzullo L, Betta P, Mosca F, Ferrari F, Magaldi R, Stronati M, Farina D; Italian Task Force for the Study and Prevention of Neonatal Fungal Infections, Italian Society of Neonatology. Bovine Lactoferrin Supplementation for Prevention of Late-Onset Sepsis in Very Low-Birth-Weight Neonates: A Randomized Trial. JAMA. 2009;302(13):1421-8.
4. Manzoni P, Dall'Agnola A, Tomé D, Kaufman DA, Tavella E, Pieretto M, Messina A, De Luca D, Bellaiche M, Mosca A, Piloquet H, Simeoni U, Picaud JC, Del Vecchio A. Role of Lactoferrin in Neonates and Infants: An Update. Am J Perinatol. 2018;35(6):561-5.
5. Pammi M. Enteral lactoferrin supplementation for prevention of sepsis and necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2017;(6):CD007137.
6. Lang J, Yang N, Deng J, Liu K, Yang P, Zhang G, Jiang C. Inhibition of SARS pseudovirus cell entry by lactoferrin binding to heparin sulfate proteoglycans. PLoS ONE. 2011;6:e23710.
7. Reghunathan R, Jayapal M, Hsu LY, Chng HH, Tai D, Leung BP, Melendez AJ. Expression profile of immune response genes in patients with severe acute respiratory syndrome. BMC Immunology. 2005;6:2.
8. Oda H, Wakabayashi H, Tanaka M, Yamauchi K, Sugita C, Yoshida H, Abe F, Sonoda T, Kurokawa M. Effects of lactoferrin on infectious diseases in Japanese summer: A randomized, double-blinded, placebo-controlled trial. J Microbiol Immunol Infect. 2020 Feb 26. [Epub ahead of print].
9. Vitetta L, Coulson S, Beck SL, Gramotnev H, Du S, Lewis S. The clinical efficacy of bovine lactoferrin/whey protein Ig-rich fraction for the common cold: a double blind randomized study. Complement Ther Med. 2013;21:164-71.
10. Wakabayashi H, Oda H, Yamauchi K, Abe F. Lactoferrin for prevention of common viral infections. J Infect Chemother. 2014;20(11):666-71.
11. Zhou J, Du J, Huang L, Wang Y, Shi Y, Lin H. Preventive effects of vitamin D on seasonal influenza A in infants: a multicenter, randomized, open, controlled clinical Trial. J Infectious Dis. 2018;37:749.