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EDITORIAL

# Lactoferrin, a Great Wall of host-defence?

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Lactoferrin (Lf) is a multifunctional iron-binding glycoprotein that is specifically produced by exocrine glands and it is also expressed at high levels in neutrophils in mammals. Since this cationic protein was first isolated from bovine milk in 1939 and subsequently shown to be the main ferric iron-binding protein in human milk (Sorensen and Sorensen 1939; Groves 1960), it has been demonstrated that Lf can be involved in numerous distinct physiological processes. Many of the biological functions that are attributed to the protein are related to host-defence. Intriguingly, this set of properties is unique to Lf and it is not shared with the closely related iron-binding transferrin protein. Today, PubMed lists nearly 10,000 papers that focus on different aspects of the Lf protein. Every two years, researchers from widely different scientific fields and backgrounds, that are interested in understanding the biological roles and the potential applications of Lf, meet and exchange information. To date, a total of fifteen such meetings have been held successfully since the first International Conference on Lactoferrin Structure, Function and Applications was convened in Honolulu in 1993. The XVth Lf conference was held for the second time in Beijing, running from December 6 to 10, 2021 (the first Lf meeting in Beijing was organized in 2009, see Wang and Tian 2010). Because of the COVID-19 pandemic it was organized as the first virtual Lf meeting. More than two hundred attendees from twenty-eight different countries, covering six continents, overcame the obvious time zone challenges that are inherent in such international virtual gatherings. Nonetheless, all the participants enjoyed the zoom-communications on lactoferrin with enthusiastic participation in the discussions and in some instances the new virtual format actually allowed for even better information exchange as the previous in-person meetings. The program was made up of a total of seventy-six oral and eleven poster presentations covering widely distinct LF topics. To start off the meeting, the basic biochemistry of Lf and its effects on coronavirus were discussed during the opening session by Dr. Hans Vogel and Dr. Piera Valenti, respectively. A total of sixteen Young Scientist Awards were handed out, and the Genevieve Spik Award, for the overall trainee winner, was presented to Dr. Carmen Mirabelli from the of University of Michigan by Dr. Bo Lönnerdal at the closing ceremony. A total of twenty-two articles, related to the science presented at the

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meeting, are now collected in this issue of the BioMetals journal, and their key findings will be briefly introduced here.

Lf is widely distributed in the body fluids of mammals and its levels are especially high in milk with concentrations around 5 g/L in human colostrum and 1 g/L in mature human milk (Vogel 2012; Demmelmair et al. 2017; Lönnerdal et al. 2021; Hao et al. 2021; Ochoa and Vogel 2021). As a highly concentrated whey protein in human milk, it has been reported that Lf could play an important role for the development of the infant (Lönnerdal 2003). In utero, the infant is rarely exposed to antigens, and hence Lf may become a major driver to promote rapid maturation of the intestinal immune system and the associated gut microbiome. As such, the protein would exert important effects on intestinal cells (Demmelmair et al. 2017). Bovine Lf (bLf) possesses high amino acid sequence homology (69%) and it displays in many cases a similar bioactivity when compared to human Lf (hLf). Consequently, many researchers make use of bLf in their studies, as it is more readily available than hLf. For example, Kubo et al. (2022) demonstrated the effects of bLf on the immune system, which significantly upregulated the expression levels of IFN-α, HLA-DR, and CD86 in plasmacytoid dendritic cells (pDCs), which in turn promoted pDC activation upon viral recognition. Various previous studies have demonstrated that oral application of Lf can affect the immune system (Wang 2000; De la Rosa et al. 2008). Piglets are usually considered as an excellent preclinical model for the study of certain human diseases (Guilloteau et al. 2010). At the meeting Ma et al. (2022) reported that bLF can play an important role in neonatal health by dietary supplementation of bLF to piglets. In these model target animals, bLf enhanced the growth performance, reduced the rate of diarrhea in weaning piglets, and improved intestinal immunity, morphology and barrier function, while balancing the intestinal microbiota. In child health, the immunomodulatory functions of Lf could represent a basic mechanism of suppressing diarrhea and regulating the microbiome (Miyakawa et al. 2022). Therefore, bLF could be widely used as a functional food ingredient (Tomita et al. 2009). In addition, Lf can prevent infection of cervical tissue in pregnant women, thus inhibiting preterm birth (PTB) and improving the prognosis for the offspring. As a prebiotic contained in breast milk, the first ever clinical application of Lf was to suppress PTB in humans (Otsuki and Imai 2017; Otsuki et al. 2022). However, an excess of Lf in the body could also cause side effects. For example, in this issue of Biometals, Estefanía et al. (2022) demonstrated that high concentrations of Lf, as caused by intraperitoneal injections, will give rise to a declining pregnancy rate in rats. It was suggested that the changes of the Lf levels could influence the reproductive process, favoring it or perhaps interfering with it, in different physiological or pathological situations. Also, Kaufman et al. (2023) studied the acceptable limits for Gram-negative bacterial LPS (lipopolysaccharide) contaminations originating from bLf fortification as one of the key ingredients in certain formula preparations; such studies are necessary to secure it is safe to include Lf in infant formulas.

Lf is an important contributor to mammalian innate immunity, as it can inhibit the growth of many pathogens. With the outbreak of the COVID-19 pandemic, studies on the effects of Lf on COVID-19 have sharply increased. Given the well-documented antiviral properties of Lf (e.g. Berlutti et al. 2011) we believe that experiments in this direction should be highly encouraged. Lf is well-known to block viral entry by interacting with heparan sulfate proteoglycans of the host cells and/or with surface components of viral particles (Burckhardt et al., 2009; Rosa et al. 2022). The study by Sokolov et al. (2022) focused on the binding of recombinant hLf to the receptor-binding domain (RBD) of the Spike protein of the SARS-CoV2 virus. Competition between hLf and the RBD of the Spike protein for binding with ligands of the transferrin receptor (TfR1) can prevent TfR1-mediated endocytosis of SARS-CoV-2 coronavirus and inhibit SARS-CoV-2 replication. Natural Lf and the well-characterized N-terminal synthetic peptide of Lf, known as lactoferricin (for a review see Gifford et al. 2005), both inhibited the proteolytic priming of the viral spike protein by transmembrane protease serine 2, thereby blocking the virus from entering the cell (Ohradanova-Repic et al. 2022). In addition, a specific recovery effect for COVID-19 patients upon Lf administration was observed via immunoregulation, anti-hypoxic and anti-anemic functions. Thus, Lf was reported as possessing a potential role in the prevention, treatment, and recovery from COVID-19 infections. Navarro et al. (2022) evaluated the effects of bLf on COVID-19 infections in hospital settings in a clinical trial, but their results showed no significant effects of bLF on COVID-19 infection incidence, severity and symptoms in hospital personnel. However, liposomal bLf was used through oral and intranasal administration in COVID-19 in patients with mild-to-moderate disease and in COVID-19 asymptomatic patients; this work suggested a potential role for bLf as significant decreases in serum ferritin, IL-6, and D-dimers levels were seen (Campione et al. 2021). Be that as it may, a recent report on a placebo-controlled clinical trial, where bLf was given to more than 200 hospitalized patients as an additive to regular COVID-19 therapy, showed no differences in the primary outcomes (Matino et al. 2023). From these conflicting results, it seems clear that further studies with larger sample size are needed to determine whether there is any future role for bLf in the treatment of COVID-19. It is worth noting that these different experimental results may to some extent be related to differences in the dosage, the interval of the administration, the iron saturation of bLf, and to other conditions that were used during the purification, storage and administration of bLf.

In addition to the antiviral work, the León-Sicairos team (Arredondo-Beltrán et al. 2023) reported results for bLF and its derived peptides against cultured HepG2 liver cancer cells and Jurkat leukemia cells. These workers showed that the bLF protein and some of its derived peptides displayed anticancer activity against such cultured cells. This work extends on earlier studies with bLf derived peptides acting on various other cultured cancer cells (e.g. Eliasson et al. 2002, 2009; Arias et al. 2017), which showed similar positive effects, although the mechanism by which these peptides cause cell death (necrosis versus apoptosis), seems to differ. In this regard it is interesting to point out, that the LTX-315 anticancer peptide, that appears to have successfully gone through initial clinical trials, was originally inspired by a host-defence peptide that was modeled directly after part of the sequence of bLf (Eike et al. 2015).

The antibacterial properties of Lf were amongst the first discovered functions of the protein, but this is still an active area of research. In this special issue, Conte et al. (2022) demonstrated that bLf can effectively inhibit cystitis caused by *Escherichia coli*, owing to competitive binding between the cationic bLf and anionic components of the host cells; this in turn may hide bacterial entrance sites and thereby inhibit bacterial invasion of the cells. Abad et al. (2022) reported that in vitro gastrointestinal digestion of bLf actually promoted the antibacterial activity of infant formulas that were supplemented with lactoferrin against *Cronobacter sakazakii*. This bacterium was selected for this study, as it is extremely resistant to dry conditions and it has been identified in previous studies as the source of infections in infants originating from contaminated powdered infant formula. Meanwhile, Lf can alleviate the Gram-negative bacterial LPS-induced acute inflammation response by suppressing the expression of the macrophage-associated chemokines CCL2 and CCL5 (Liu et al. 2022). Both hLf itself and hLf attached to an Fc domain of human IgG2 could treat *Mycobacterium tuberculosis* primary infections and modulate the immune related development of the pathology (Actor et al. 2022). Taken together, these studies validate the potential of Lf as an antibiotic alternative against bacteria, especially for antibiotic-resistant pathogens.

Lf, as a member of the transferrin family, can also play an important role in animal physiology in terms of its potent ferric iron-binding capabilities. In an intervention study in infants with a high risk of anemia bLf could promote dietary iron absorption, leading to a lower prevalence of anemia and other related diseases (Miyakawa et al. 2022). Also, bLf can help to cure β-thalassemia in women through its ability to decrease IL-6 synthesis. Lf, as an important factor to maintain iron metabolism and homeostasis, possesses the property to regulate iron disorders that are associated with different pathologies (Ianiro et al. 2022). Although holo- and apo-Lf often display similar bioactivities, the different localization of holo- and apo-Lf in the cell may suggest a different mode of action for Lf with different levels of iron saturation (Jenssen et al. 2008). Also, it was reported that an FcLf adduct, created from hLf that was fused with an Fc domain of IgG, strongly induced expression of PI3K, with subsequent activation of the AKT/mTOR signaling pathway (Zaczyńska et al. 2022). In addition, Lf not only provides ferric iron for mammals, but it can also be used as a donor by some pathogenic bacteria (Chan et al. 2022). These workers revealed molecular level details about the mechanism of iron transport in *Moraxella catarrhalis* by analyzing the crystal structures of the *M. catarrhalis* FbpA in the holo- and apo-conformations.

After the original discovery of Lf, now more than 80 years ago, at least twenty different biological functions have been described in the scientific literature. New functions continue to be uncovered, for example Lf was recently shown to be a natural inhibitor of plasminogen activation (Zwirzitz et al. 2018), indicating that the protein may actually play a role during the dissolution of blood clots. At the meeting Kraaij et al. (2022) presented new data to show that Lf appears to be involved in the formation of salivary stones, a condition that may lead to blockage of the salivary duct. In terms of applications, the purified Lf protein has been widely used in studies involving nutrition, animal husbandry and clinical treatments for various diseases. This wide range of applications has unfortunately created some confusion in research and development, as products of widely different origin (e.g. hLf or bLf), purity, stability and iron-saturation have been used. Thus, in future communications, Lf products should be better characterized, so that results may be more easily compared (Lönnerdal et al. 2021). The use of Lf should also be classified as accurately as possible: (a) As a nutraceutical food supplement to regulate immunity, iron storage, transport and release for special populations (neonates, infants, toddlers, children, adults, etc.); (b) As a feed additive for livestock, poultry and fish, improving the growth performance and regulating intestinal flora (although at current prices the costs for such applications would be too high); (c) As a clinical drug candidate for the treatment of human diseases such as cancer or inflammatory and infectious diseases (Vogel 2012; Chen et al. 2022; Hopp et al. 2022; Nopia et al. 2022). As examples of potential future clinical applications of Lf, here Chen et al. (2022) discuss a role for Lf during atherosclerosis, while Nopia et al. (2022) describe an interesting new albumin-hLf fusion protein that has improved pharmacokinetic properties for clinical applications, particularly in the area of cancer. Finally, Hopp et al. (2022) delineate very careful proteolysis and stability studies describing degradation of bLf in vaginal fluids, a bodily location where this protein may have strong antibacterial effects, through its potent iron-binding properties.

Purified bLf product is mainly obtained from milk whey by dairy producers using traditional biochemical separation and extraction techniques. Spray drying is sometimes used to create a dry and stable product, but such processing techniques could affect the integrity of the protein. Clearly, different approaches used for the purification and storage of the protein can lead to significant differences in the product and its iron saturation levels, resulting in challenges for standard testing of the quality of the final Lf product (Lönnerdal et al. 2021). Recombinant expression of Lf might be considered as a novel way forward to create a more consistent higher quality product (Lönnerdal 2002; Bai et al. 2010; Zhao et al. 2013), but at the moment this is not yet a commercially viable alternative. Short peptides derived from Lf as drug candidates are a promising avenue for some applications (Eike et al. 2015; Hao et al. 2017), and these can be obtained with different functional groups via truncation, modification and other strategies by means of de-novo design, and biotechnological and chemical processing methods. As reported at the meeting, the oral administration mode markedly influences Lf bioavailability, and nano drug carriers may be particularly suited as different delivery modes of LF for different therapies (Ong et al. 2022). Overall, more attention should be paid to such factors, so that the rational development and application of lactoferrin can start to make contributions to health management, nutritional regulation and host-defense improvements in terms of the One-Health concept.

In closing, we would like to sincerely thank all the meeting participants including all the attendees, our sponsors and the local organizers, including the team staff, the host Institute and the Chinese Academy of Agricultural Sciences. We also thank the International Scientific Committee as well as all the authors and reviewers for their contributions to the work presented in this special issue, as well as the editorial staff of BioMetals. Finally, we wish continued success to the upcoming 16th Lactoferrin conference in Rome, which will take place in-person in early November, 2023.

## References

Abad I, Serrano L, Graikini D et al (2022) Effect of in vitro gastrointestinal digestion on the antibacterial activity of bioactive dairy formulas supplemented with lactoferrin against *Cronobacter sakazakii*. Biometals. https://doi.org/10.1007/s10534-022-00459-5

Actor JK, Nguyen TKT, Wasik-Smietana A, Kruzel ML (2022) Modulation of TDM-induced granuloma pathology by human lactoferrin: a persistent effect in mice. BioMetals. https://doi.org/10.1007/s10534-022-00434-0

Arias M, Hilchie AL, Haney EF, Bolscher JG, Hyndman ME, Hancock RE, Vogel HJ (2017) Anticancer activities of bovine and human lactoferricin-derived peptides. Biochem Cell Biol 95(1):91–98. https://doi.org/10.1139/bcb-2016-0175

Arredondo-Beltrán IG, Ramírez-Sánchez DA, Zazueta-García JR, Canizalez-Roman A, Angulo-Zamudio UA, Velazquez-Roman JA, Bolscher JGM, Nazmi K, León-Sicairos N (2023) Antitumor activity of bovine lactoferrin and its derived peptides against HepG2 liver cancer cells and jurkat leukemia cells. Biometals. https://doi.org/10.1007/s10534-022-00484-4

Bai X, Teng D, Tian Z, Zhu Y, Yang Y, Wang J (2010) Contribution of bovine lactoferrin inter-lobe region to iron binding stability and antimicrobial activity against *Staphylococcus aureus*. BioMetals 23(3):431–9. https://doi.org/10.1007/s10534-010-9300-x

Berlutti F, Pantanella F, Natalizi T, Frioni A, Paesano R, Polimeni A, Valenti P (2011) Antiviral properties of lactoferrin–a natural immunity molecule. Molecules 16(8):6992–7018. https://doi.org/10.3390/molecules16086992

Burckhardt CJ, Greber UF (2009) Virus movements on the plasma membrane support infection and transmission between cells. PLoS Pathog 5:e1000621

Campione E, Lanna C, Cosio T et al (2021) Lactoferrin as antiviral treatment in COVID-19 management: preliminary evidence. Int J Environ Res Public Health 18(20):10985. https://doi.org/10.3390/ijerph182010985

Chan C, Ng D, Fraser ME, Schryvers AB (2022) Structural and functional insights into iron acquisition from lactoferrin and transferrin in Gram-negative bacterial pathogens. BioMetals. https://doi.org/10.1007/s10534-022-00466-6

Chen C, Lu M, Zhang Z (2022) Qin L The role of lactoferrin in atherosclerosis. BioMetals. https://doi.org/10.1007/s10534-022-00441-1

Conte AL, Longhi C, Conte MP et al (2022) Effect of bovine lactoferrin on recurrent urinary tract infections: in vitro and in vivo evidences. BioMetals. https://doi.org/10.1007/s10534-022-00409-1

De la Rosa G, Yang D, Tewary P et al (2008) Lactoferrin acts as an alarmin to promote the recruitment and activation of APCs and antigen-specific immune responses. J Immunol 180:6868–6876. https://doi.org/10.4049/jimmunol.180.10.6868

Demmelmair H, Prell C, Timby N, Lönnerdal B (2017) Benefits of lactoferrin, osteopontin and milk fat globule membranes for infants. Nutrients 9:817. https://doi.org/10.3390/nu9080817

Eike LM, Yang N, Rekdal Ø, Sveinbjørnsson B (2015) The oncolytic peptide LTX-315 induces cell death and DAMP release by mitochondria distortion in human melanoma cells. Oncotarget 6(33):34910–34923. https://doi.org/10.18632/oncotarget.5308

Eliassen LT, Berge G, Sveinbjørnsson B, Svendsen JS, Vorland LH, Rekdal Ø (2002) Evidence for a direct antitumor mechanism of action of bovine lactoferricin. Anticancer Res 22(5):2703–2710 PMID: 12529985

Eliassen LT, Berge G, Leknessund A, Wikman M, Lindin I, Løkke C, Ponthan F, Johnsen JI, Sveinbjørnsson B, Kogner P, Flaegstad T, Rekdal Ø (2006) The antimicrobial peptide, lactoferricin B, is cytotoxic to neuroblastoma cells in vitro and inhibits xenograft growth in vivo. Int J Cancer 119(3):493–500. https://doi.org/10.1002/ijc.21886

Estefanía M, Aldana G, Marianela M et al (2022) Lactoferrin affects in vitro and in vivo fertilization and implantation in rats. BioMetals. https://doi.org/10.1007/s10534-022-00460-y

Gifford JL, Hunter HN, Vogel HJ (2005) Lactoferricin: a lactoferrin-derived peptide with antimicrobial, antiviral, antitumor and immunological properties. Cell Mol Life Sci 62(22):2588–2598. https://doi.org/10.1007/s00018-005-5373-z

Groves ML (1960) The isolation of a red protein from milk. J Am Chem Soc 82:3345–3350

Guilloteau P, Zabielski R, Hammon HM, Metges CC (2010) Nutritional programming of gastrointestinal tract development. Is the pig a good model for man? Nutr Res Rev 23(1):4–22. https://doi.org/10.1017/S0954422410000077

Hao Y, Yang N, Wang X, Teng D, Mao R, Wang X, Li Z, Wang J (2017) Killing of *Staphylococcus aureus* and *Salmonella enteritidis* and neutralization of lipopolysaccharide by 17-residue bovine lactoferricins: improved activity of Trp/Ala-containing molecules. Sci Rep 7:44278. https://doi.org/10.1038/srep44278

Hao Y, Wang J, Teng D, Wang X, Mao R, Yang N, Ma X (2021) A prospective on multiple biological activities of lactoferrin contributing to piglet welfare. Biochem Cell Biol 99(1):66–72. https://doi.org/10.1139/bcb-2020-0078

Hopp TP, Matthews MH, Spiewak K et al (2022) Proteolysis of vaginally administered bovine lactoferrin: clearance, intersubject variability, and implications for clinical dosing. BioMetals. https://doi.org/10.1007/s10534-022-00481-7

Ianiro G, Rosa L, Bonaccorsi di Patti MC, Valenti P et al (2022) Lactoferrin: from the structure to the functional orchestration of iron homeostasis. BioMetals. https://doi.org/10.1007/s10534-022-00453-x

Jenssen H, Sandvik K, Andersen JH et al (2008) Inhibition of HSV cell-to-cell spread by lactoferrin and lactoferricin. Antiviral Res 79(3):192–198. https://doi.org/10.1016/j.antiviral.2008.03.004

Kaufman DA, Perks PH, Greenberg RG, Jensen D (2023) Endotoxin content in neonatal formulas, fortification, and lactoferrin products: association with outcomes and guidance on acceptable limits. Biometals. https://doi.org/10.1007/s10534-022-00487-1

Kraaij S, de Visscher JGAM, Apperloo RC, Nazmi K, Bikker FJ, Brand HS (2022) Lactoferrin and the development of salivary stones: a pilot study. Biometals. https://doi.org/10.1007/s10534-022-00465-7

Kubo S, Miyakawa M, Tada A, Oda H et al (2022) Lactoferrin and its digestive peptides induce interferon-α production and activate plasmacytoid dendritic cells ex vivo. BioMetals. https://doi.org/10.1007/s10534-022-00436-y

Liu C, Peng Q, Wei L et al (2022) Deficiency of lactoferrin aggravates lipopolysaccharide-induced acute inflammation via recruitment macrophage in mice. Biometals. https://doi.org/10.1007/s10534-022-00398-1

Lönnerdal B (2002) Expression of human milk proteins in plants. J Am Coll Nutr 21:218S-221S. https://doi.org/10.1080/07315724.2002.10719269

Lönnerdal B (2003) Nutritional and physiologic significance of human milk proteins. Am J Clin Nutr 77:1537s–1543s. https://doi.org/10.1093/ajcn/77.6.1537S

Lönnerdal B, Du X, Jiang R (2021) Biological activities of commercial bovine lactoferrin sources. Biochem Cell Biol 99(1):35–46. https://doi.org/10.1139/bcb-2020-0182

Ma X, Hao Y, Mao R, Yang N, Zheng X, Li B, Wang Z, Zhang Q, Teng D, Wang J (2022) Effects of dietary supplementation of bovine lactoferrin on growth performance, immune function and intestinal health in weaning piglets. Biometals. https://doi.org/10.1007/s10534-022-00461-x

Matino E, Tavella E, Rizzi M, Avanzi GC, Azzolina D, Battaglia A, Becco P, Bellan M, Bertinieri G, Bertoletti M, Casciaro GF, Castello LM, Colageo U, Colangelo D, Comolli D, Costanzo M, Croce A, D'Onghia D, Della Corte F, De Mitri L, Dodaro V, Givone F, Gravina A, Grillenzoni L, Gusmaroli G, Landi R, Lingua A, Manzoni R, Marinoni V, Masturzo B, Minisini R, Morello M, Nelva A, Ortone E, Paolella R, Patti G, Pedrinelli A, Pirisi M, Ravizzi L, Rizzi E, Sola D, Sola M, Tonello N, Tonello S, Topazzo G, Tua A, Valenti P, Vaschetto R, Vassia V, Zecca E, Zublena N, Manzoni P, Sainaghi PP (2023) Effect of lactoferrin on clinical outcomes of hospitalized patients with COVID-19: the LAC randomized clinical trial. Nutrients 15(5):1285. https://doi.org/10.3390/nu15051285

Miyakawa M, Oda H, Tanaka M (2022) Clinical research review: usefulness of bovine lactoferrin in child health. Biometals. https://doi.org/10.1007/s10534-022-00430-4

Navarro R, Paredes JL, Tucto L et al (2022) Bovine lactoferrin for the prevention of COVID-19 infection in health care personnel: a double-blinded randomized clinical trial (LF-COVID). BioMetals. https://doi.org/10.1007/s10534-022-00477-3

Nopia H, Kurimoto D, Sato A (2022) Albumin fusion with human lactoferrin shows enhanced inhibition of cancer cell migration. BioMetals. https://doi.org/10.1007/s10534-022-00447-9

Ochoa TJ, Vogel HJ (2021) Lactoferrin extends its reach into South America. Biochem Cell Biol 99(1):v–vii. https://doi.org/10.1139/bcb-2021-0025

Ohradanova-Repic A, Skrabana R, Gebetsberger L et al (2022) Blockade of TMPRSS2-mediated priming of SARS-CoV-2 by lactoferricin. Front Immunol 13:958581. https://doi.org/10.3389/fimmu.2022.958581

Ong R, Cornish J, Wen J (2022) Nanoparticular and other carriers to deliver lactoferrin for antimicrobial, antibiofilm and bone-regenerating effects: a review. BioMetals. https://doi.org/10.1007/s10534-022-00455-9

Otsuki K, Imai N (2017) Effects of lactoferrin in 6 patients with refractory bacterial vaginosis. Biochem Cell Biol 95:31–33. https://doi.org/10.1139/bcb-2016-0051

Otsuki K, Nishi T, Kondo T et al (2022) Review, role of lactoferrin in preventing preterm delivery. BioMetals. https://doi.org/10.1007/s10534-022-00471-9

Rosa L, Cutone A, Conte MP, Campione E, Bianchi L, Valenti P (2022) An overview on in vitro and in vivo antiviral activity of lactoferrin: its efficacy against SARS-CoV-2 infection. BioMetals. https://doi.org/10.1007/s10534-022-00427-z

Sokolov AV, Isakova-Sivak IN, Mezhenskaya DA, Kostevich VA, Gorbunov NP, Elizarova AY, Matyushenko VA, Berson YM, Grudinina NA, Kolmakov NN, Zabrodskaya YA, Komlev AS, Semak IV, Budevich AI, Rudenko LG, Vasilyev VB (2022) Molecular mimicry of the receptor-binding domain of the SARS-CoV-2 spike protein: from the interaction of spike-specific antibodies with transferrin and lactoferrin to the antiviral effects of human recombinant lactoferrin. Biometals 5:1–26. https://doi.org/10.1007/s10534-022-00458-6

Sorensen M, Sorensen SPL (1939) The proteins in whey. Comptes-rendus des Trav. du Lab. Carlsberg. 23:55–99

Tomita M, Wakabatashi H, Shin K et al (2009) Twenty-five years of research on bovine lactoferrin applications. Biochimie 91:52–57. https://doi.org/10.1016/j.biochi.2008.05.021

Vogel HJ (2012) Lactoferrin, a bird's eye view. Biochem Cell Biol 90(3):233–244. https://doi.org/10.1139/o2012-016Epub 2012 Apr 27

Wang WP (2000) Activation of intestinal mucosal immunity in tumor-bearing mice by lactoferrin. Jpn J Cancer Res 91:1022–1027. https://doi.org/10.1111/j.1349-7006.2000.tb00880.x

Wang J, Tian Z (2010) Recent advances in lactoferrin research and development during the past two years (2007–2009): in lieu of a preface of the Special Issue Lactoferrin. BioMetals 23(3):355–357. https://doi.org/10.1007/s10534-010-9303-7

Zaczyńska E, Kocięba M, Artym J et al (2022) A cytotoxic effect of human lactoferrin fusion with fc domain of IgG. BioMetals. https://doi.org/10.1007/s10534-022-00443-z

Zhao J, Xu JX, Wang JW, Li N (2013) Lactation performance and milk nutritional composition analysis of human lactoferrin transgenic cows. Transgenic Res 22:228

Zwirzitz A, Reiter M, Skrabana R, Ohradanova-Repic A, Majdic O, Gutekova M, Cehlar O, Petrovčíková E, Kutejova E, Stanek G, Stockinger H, Leksa V (2018) Lactoferrin is a natural inhibitor of plasminogen activation. J Biol Chem 293(22):8600–8613. https://doi.org/10.1074/jbc.RA118.003145