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Biochemistry, Pathophysiology and Clinical Significance of Lactoferrin: A Review Article

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ABSTRACT

Lactoferrin is a multi-iron binding functional glycoprotein with significant clinical applications in the treatment of infectious diseases, inflammatory disorders, cancer, neonatology, and metabolic conditions. Its normal function involves high affinity iron sequestration complementary direct microbial membrane interactions making it an important part of the innate immune system. Clinically proven effective in lactoferrin supplementation to reduce neonatal infections on sepsis as well as necrotizing enterocolitis; this will be a promising prophylactic approach for preterm infants. Its antiviral activity broadens even more its therapeutic potency regarding emerging viral infections including some preliminary applications on COVID-19. It is reported that the immunomodulatory lactoferrin regulates both processes by controlling cytokine production and cell function. Fecal lactoferrin is an easy-to-apply inflammation marker within the intestines for inflammatory bowel disease besides being helpful in monitoring how well treatment is working. Apart from these functions, lactoferrin can exert anticancer activity via antiproliferative, pro-apoptotic as well as anti-angiogenic mechanisms. Newer evidences also support its application as an adjuvant in cancer therapy. Additionally, lactoferrin has a role in neonate development through gut maturation plus immune system education. Disorder management, especially metabolic, cardiovascular, and diabetic related disorders, seems to be where lactoferrin aces it by modulating iron homeostasis plus reducing oxidative stress. The challenges of the bioavailability and standardized preparations of lactoferrin limit the therapeutic promise it holds. Further advances in delivery technologies, together with expanded clinical trials, are needed to optimize its use.

KEYWORDS

Lactoferrin, immunomodulatory, cancer, neonatal infections.

Introduction

Biochemistry is the study of chemical processes and substances that take place within living organisms. Since health and disease are at the molecular level, this discipline is central to understanding them. Among many

biomolecules important for human physiology, one should consider glycoproteins from a family of multifunctional iron-binding ones - lactoferrin (Legrand, 2016). It was isolated first from Bovine milk in early 1960s. After that, lactoferrin was discovered in many mammalian secretions-saliva, tears, and mucosal secretions which emphasize its primary role in host defense (Ward et al., 2005). Complexity and myriad functions render a protein such as lactoferrin worthy of significant review in biochemical subject matter.

Lactoferrin is considered mainly as a biochemical protein because it binds iron in the ferric form (Fe3+) with high affinity for the homeostatic control of iron and limitation of microbial growth by providing siderophilic microbes with unavailable iron (González-Chávez, Arévalo-Gallegos, & Rascón-Cruz, 2009). Along with this iron-chelating aspect, lactoferrin can also contact diverse cellular receptors, initiate different immune responses, and directly inhibit bacteria, viruses, or fungi from growing (Actor, Hwang & Kruzel, 2009). Thus it has crucial roles not in only mucosal immunology but systemic immune regulation as an important element of innate immunity.

The disease states relevant to the pathophysiology of lactoferrin are varied. Some infectious diseases, inflammatory conditions, cancer, and metabolic syndromes have previously reported aberrations in the levels of this protein (Legrand, 2016). Indicatively Inflammatory Bowel Diseases like Crohn's disease and Ulcerative Colitis reported that fecal lactoferrin as a very sensitive biomarker for any intestinal inflammation thus bridging biochemical characteristics with clinical applications (Mäkitalo et al., 2016). In addition to what has already been established regarding anti-inflammatory and immunomodulatory effects that have led therapeutic potential investigations to use it as a natural therapy for infections and chronic inflammatory conditions got antibiotic resistance increasing concern (Kruzel, Zimecki, & Actor, 2017).

Owing to the rapidly expanding lactoferrin literature—in molecular biology, immunology, microbiology, and clinical medicine—a review that sums up what is currently known and directs future research should be typified as comprehensive. A review of this sort would perform several critical functions in that it would bring together otherwise little consolidated data on the subject from different disciplines; orient clinicians on the diagnostic and therapeutic applicability of lactoferrin; point out where further study is needed because of either a gap or controversy; and encourage translational research moving bench science into practice (Legrand, 2016).

The infectious and inflammatory diseases place a large amount of burden on the globe, so it is urgent to look into bioactive molecules such as lactoferrin. Because it comes naturally, it is safe and has many different actions, making it a good choice for new treatments (Actor et al., 2009). For example, recent studies showed lactoferrin able to fight viruses that cause them in today's times, like COVID-19; thus showing its possible use as an additional treatment (Huang et al., 2020).

At the biochemical level, lactoferrin continues to attract much research interest in structure-function relationships. Information on how its iron-binding lobes glycosylate and interact with cellular receptors to modulate activity could guide the synthesis of peptides derived from lactoferrin with improved efficacy and stability (González-Chávez et al., 2009). Moreover, an effect of lactoferrin on gut microbiota and mucosal immunity paves new ways for exploring its role in microbial homeostasis and disease conditions related to dysbiosis Legrand (2016).

Accordingly, lactoferrin is a high priority glycophosphoprotein of great importance both biochemically and clinically in which multiple functions concerning the protection of the host, immune modulation, and the pathophysiology of diseases justify intense academic interest. Writing an exhaustive review article on lactoferrin will not only bring together a large amount of knowledge that is changing quickly but also help to create new research and clinical applications aimed at improving health results all over the world.

Biochemical properties and metabolism of lactoferrin

Lactoferrin is a member of the transferrin family glycoproteins that are usually known to bind ferric ions (Fe3+) with conjugate affinity; hence, iron-binding activity is normally related to it. Many biological roles from this antimicrobial action arise in the system of iron homeostasis since the bacterium also requires iron to grow. Apart from enzymatic activities, many other related factors stem from cell receptors and immune response modulation. The biochemical properties and metabolism of lactoferrin should be well elaborated to appreciate its physiological importance and therapeutic potential (Legrand, 2016).

Structure and Binding of Iron

Lactoferrin is an 80-kDa glycoprotein composed of a single polypeptide chain of approximately 700 amino acids organized into two homologous lobes the N-lobe and the C-lobe each capable of binding one ferric ion with binding one ferric ion with lactoferrin has high affinity (Baker & Baker, 2009). The iron binding site in each lobe conserved amino acid residue coordinate ferric iron synergistically with a carbonate anion stabilizes the complex Legrand (2016). This allows lactoferrin to bind iron reversibly so that it can function as an iron carrier and at the same time it can deprive pathogens of the iron for their growth.

The iron-binding capacity of lactoferrin is pH dependent; it binds iron tightly at neutral and alkaline pH it releases at acidic pH. This property is critical for iron transport and release in biological systems (González-Chávez, Arévalo-Gallegos, & Rascón-Cruz, 2009). The glycosylation pattern of lactoferrin further affects its stability half-life, and interactions with other molecules. Human lactoferrin typically contains three to four N-linked glycosylation sites varying in oligosaccharide composition and consequently proteolysis resistance as well as receptor binding (Baker & Baker, 2009).

Biochemical Actions Beyond Iron Binding

Although iron chelation has long been regarded as the primary biochemical contribution of lactoferrin, it is much more than that. Ribonuclease and DNase enzymatic activities are also included, which in fact enhance the antimicrobial property by degrading the nucleic acids of any microbial organism (Actor et al., 2009). In addition to this, it can also recognize and bind to Gram-negative bacterial surface LPS thus neutralizing endotoxin effects and it is anti-inflammatory (Ward et al., 2005).

Another important biochemical property is the interaction with cellular receptors. Epithelial and immune cells show sensitivity by expressing on them specific receptors for lactoferrin such as the lactoferrin receptor (LfR), low-density lipoprotein receptor-related protein-1 (LRP1), and intelectin-1 (Laursen & Moestrup, 2009). This allows its internalization and modulation of cell signaling pathways along with regulation at the level of gene expression that impacts immune responses as well as cell proliferation and apoptosis (Legrand, 2016).

Lactoferrin is mainly produced by epithelial cells of glands and neutrophils. In humans, it is strongly present in colostrum and milk. Its concentration can reach up to 7 g/L in colostrum it diminishes in mature milk (Brock, 2012). Apart from milk, lactoferrin is present in saliva, tears, nasal secretions, mucus of the bronchi, and the gastrointestinal tract which shows its general physiological importance (González-Chávez et al., 2009). Lactoferrin resists degradation when taken orally in the stomach's acidic environment due to its stable structure and glycosylation; it achieves the intestine mostly intact (Brock, 2012). In the intestine, Lf may be absorbed by enterocytes through receptor-mediated endocytosis using specific receptors (LfR) and other pathways (González-Chávez et al., 2009). After internalization, it can act locally as an antimicrobial and mucosal immune response modulator or be transported into circulation where it contributes to systemic effects.

The plasma half-life of lactoferrin is fairly short, assumed to be about 8 hours since it is quickly taken up by the liver and kidney (Baker & Baker, 2009). Metabolism of lactoferrin includes proteolytic breakdown by enzymes like trypsin and pepsin from the gastrointestinal tract plus lysosomal enzymes from the cell. It is quite fascinating because even peptides resulting from the proteolysis of lactoferrin continue to possess biological activity; for instance, lactoferricin, a peptide from the N-lobe has strong antimicrobial as well as immunomodulatory actions (Actor et al., 2009).

Control of lactoferrin action

Lactoferrin gene expression is normally regulated at both transcriptional and post-transcriptional levels. Synthesis of this protein is normally modulated by a wide array of stimuli, such as infections and inflammatory signals. For example, interleukin-1 (IL-1) and tumor necrosisalpha (TNF-α) cytokines increase the expression of lactoferrin in neutrophils as well as epithelial cells; therefore its production is tied to the host defense mechanism (Legrand, 2016). Estrogen Hormone can also raise the levels of lactoferrin which explains why higher concentrations are observed in milk from breasts during lactation (Brock, 2012).

Functional Implications of Biochemical Properties

The biochemical mechanisms of lactoferrin underlie the various important physiological functions it plays. The iron-binding capacity of this protein allows it to inhibit

microbial proliferation and thus it is included in first-line defense molecules at mucosal surfaces (Ward et al., 2005). This involves responses against bacterial endotoxins and immune-cell activity that eventually controls inflammatory responses and restoration of tissue homeostasis (Actor et al., 2009). Besides, interactions with host cells have consequences in a number of different processes from wound healing to cell proliferation and even differentiation (Legrand, 2016). The metabolic fate of lactoferrin, its partial resistance to degradation and the peptides generated from it, further broaden its functional repertoire. Peptides from lactoferrin have the ability to penetrate bacterial membranes and then disrupt membrane integrity; they may also stimulate host defense mechanisms (González-Chávez et al., 2009).

The clinical application of lactoferrin should be based on an understanding of its biochemistry and metabolism. Possible uses for supplementation, including lactoferrin, have been discussed in terms of its potential benefits for neonate nutrition, infectious diseases, cancer therapy, and inflammatory disorders (Kruzel et al., 2017). Supplements for oral use proved to be effective in lowering these two conditions- neonatal sepsis and necrotizing enterocolitis (Manzoni et al., 2012). Absorption and metabolism pharmacokinetics of lactoferrin prove how important the optimal dosing regimen and way of delivery are. Recombinant lactoferrin and peptides based on lactoferrin are also synthesized as treatment agents owing to their wide-range antimicrobial as well as immunomodulatory actions. This has opened the way for Actor et al. (2009) to discuss in detail novel therapeutics based on lactoferrin with enhanced stability and efficacy, achievable through detailed knowledge of both structure and metabolism.

Clinical Significance of Lactoferrin

Lactoferrin (LF) is a multifunctional iron-binding glycoprotein that has practically flooded with attention due to its immense clinical implications in the conditions of disease and wellness. Apart from the well-established biochemical roles of lactoferrin in iron metabolism and innate immunity, its clinical relevance seems to reach infectious diseases, inflammatory disorders, oncology, neonatology, and metabolic conditions. Such a wide spectrum of clinical significance places lactoferrin as a biomolecule of great interest in diagnostic and therapeutic fields.

Role in Infectious Illnesses

Antimicrobial properties constitute one of the most clinically relevant applications of lactoferrin that has been studied in great detail. Powerful antibacterial, antiviral, antifungal, and antiparasitic activities have been proved to be exercised by lactoferrin. It is a natural defense molecule that fights against infections (Ochoa & Cleary, 2009). This activity binds iron that is free and does not allow any space for the pathogens to occupy against this essential microbial growth resource (Sánchez, Calvo & Brock, 1992). The antimicrobial activity of lactoferrin can also be enhanced. Direct action on microbial surface contact can destroy cell membranes and neutralize endotoxins thereby also attacking microbes with multiple mechanisms (Gifford, Hunter & Vogel 2005).

Lactoferrin supplementation has been clinically proven to be effective in the management and treatment of neonatal infections. A premature infant is sepsis and lactoferrin oral entertaining random administration necrotizing a significant causative of late-onset sepsis, lactoferrin, and infants for necrotizing enterocolitis (NEC). Therefore, it could be presumed that lactoferrin supplements might reduce the risks since they have an obvious protective role against these high-risk conditions (Manzoni et al., 2009; Pammi & Suresh, 2017). These findings have propelled lactoferrin into clinical trials to this extent and beyond to routine use in some NICUs as a safe adjunct prophylactic agent.

Lactoferrin's antiviral properties are of clinical relevance, particularly in the recent emergence of novel viral pathogens. It inhibits viral entry and replication through mechanisms blocking viral receptors, modulating host immune responses, and interfering with viral RNA synthesis (Legrand et al., 2020). Enveloped viruses and immune enhancement- results that support lactoferrin as an adjunct treatment during the COVID-19 pandemic. Preliminary studies have brought forth lactoferrin due to its broad antiviral activity Chang et al., 2020.

Lactoferrin modulates the immune system by controlling inflammatory and autoimmune diseases. It controls cytokine production and mediators of inflammation, and also enhances the anti-inflammatory response to maintain homeostasis of the immune system (Kruzel, Zimecki, & Actor, 2017). Such attributes can have far-reaching clinical implications in conditions characterized

by overactive or chronic inflammation. For instance, in terms of inflammatory bowel disease (IBD) lactoferrin has been detected in significant amounts in diseases such as Crohn's and Ulcerative colitis. Fecal lactoferrin proves to be an easy and invasive reliable indicator for the inflammation of the intestines; it also aids in the diagnosis of diseases as well as monitoring and evaluating the efficacy of treatment(Gisbert & McNicholl, 2009). Raised levels of fecal lactoferrin correlate very well with both endoscopic and histologic activity therefore helpful to a clinician concerning mucosal healing assessment as well as therapy guidance(Mäkitalo et al., 2016).

On the other hand, it has been proven that lactoferrin supplementation has anti-inflammatory effects. In periodontal disease patients' studies lactoferrin is thought to reduce local inflammation as well as bacterial load which in turn improves clinical outcome. Therefore, it may have an ability to modulate immune responses as seen in rheumatoid arthritis and other autoimmune diseases but more research is required to develop therapeutic protocols (Kao et al., 2015; Actor et al., 2009).

Lactoferrin may show anticancer properties by stopping cell growth, promoting programmed cell death, inhibiting new blood vessel formation feeding tumors, and boosting immune responses which would help fight against tumor development and spread(Gibbons et al., 2015). The possible mechanisms for these anticancer activities include modulation of the cell cycle regulators and induction of apoptosis in cancer cells, as well as enhancement of natural killer (NK) cell and T-cell functions(Legrand, 2016).

Clinical trials and experimental studies have tested lactoferrin as a supportive treatment for many cancers, such as that of the breast, colon, and lungs. Oral or systemic administration of lactoferrin reduces tumor size as well as metastasis and increases survival in animal models and early-phase clinical studies (Gibbons et al., 2015; Nibbering, 2006). Furthermore, the modulation by lactoferrin of the tumor microenvironment especially its anti-inflammatory and anti-oxidative actions would rationalize its application therapeutically (Kruzel et al., 2017). Lactoferrin is being investigated as an adjuvant to conventional cancer therapy. Its immunomodulatory action may counteract chemotherapy-induced immunosuppression and improve the quality of life of patients (Actor et al., 2009). But clinical evidence is still at an early stage, much larger controlled trials are needed to test these claims and establish proper treatment regimens.

Neonatal and Pediatric Health

High concentrations of lactoferrin in colostrum and breast milk prove its importance in the immunity and development of neonates. Lactoferrin-mediated protection through breastfeeding protects neonates from infections while promoting the maturation of their immune system (Lönnerdal, 2009). In preterm infants, where the transfer of maternal antibodies is inadequate, supplementation with lactoferrin replaces immune deficits and lowers morbidity as well as mortality due to infections (Manzoni et al., 2009). Apart from infection control, lactoferrin encourages the growth and functioning of the intestine. It supports enterocytes to grow and differentiate, strengthens the gut barrier, and controls gut bacteria which is important for nutrient uptake and stimulating immunity (Chierici et al., 1994). Allergic diseases plus a role for lactoferrin in promoting neurodevelopmental outcomes should be further areas of investigation since clinical studies have only suggested these (Lönnerdal, 2010).

Metabolic & Systemic Disorders

Recent studies have brought the metabolic and systemic diseases aspects to lactoferrin's clinical importance. For example, lactoferrin seems to regulate iron metabolism diseases, such as chronic disease anemia. In controlling both the availability of iron and inflammatory conditions, lactoferrin could help correct iron deficiency while also reducing the damage that oxidation causes free iron to induce. Lactoferrin-anti-inflammatory and antioxidant may also properties have implications for cardiovascular diseases, metabolic syndrome, and diabetes. Experimental models demonstrate that lactoferrin reduces oxidative stress and inflammation in vascular tissues. It may slow atherosclerosis progression (Bruni et al., 2016). In diabetes, lactoferrin improves glycemic control and reduces complications through immunomodulation as well as protection against oxidative damage (Tian et al., 2015).

The applications of lactoferrin in the clinic include both diagnostics and therapeutics. Diagnostic assays for lactoferrin in biological fluids like feces, saliva, and vaginal secretions readily provide non-invasive means whereby infections, inflammation, and mucosal damage

might be detected (Gisbert & McNicholl, 2009). This is such an example: a gastroenterology clinic patient usually undergoes testing for fecal lactoferrin to differentiate between inflammatory bowel disease and irritable bowel syndrome; this eliminated an invasive procedure since colonoscopy was no longer deemed necessary (Mäkitalo et al., 2016). Lactoferrin is promoted as a dietary supplement and functional food immune support. Clinical trials document its safety and efficacy in enhancing immune function, reducing infection rates, and modulating inflammation (Kruzel et al., 2017). Its addition to infant formulas intended to replicate the protective effects of human breast milk(Lönnerdal, 2010). Also, leaps in biotech have made it easier to create recombinant human lactoferrin that's pure and active, helping clinical uses. Lactoferrin and its offshoots are being made as topical treatments for healing wounds, helping with oral health, skin issues, and also as systemic therapies (Wakabayashi, Oda, & Yamauchi, 2014).

Challenges and Future Perspectives

Even with promising clinical results, many challenges remain in exploiting lactoferrin's potential to the fullest. The variability of sources, dosages, and formulations of lactoferrin confounds the interpretation of clinical studies. Moreover, its fairly short half-life and sensitivity to proteolytic degradation raise issues of bioavailability particularly for oral administration. Future research should concentrate on systems for delivering lactoferrin, particularly encapsulation or conjugation with nanoparticles to improve stability as well as target specificity (Zhao et al., 2019). Results notwithstanding, initiatives toward large-scale and well-designed clinical trials are highly recommended to test the real efficacy of lactoferrin in diverse conditions and, further, to work out standardized therapeutic protocols. Combining lactoferrin study with individual health methods, which involve genetic and microbial analysis, might reveal custom treatments that maximize its medical good effects. Also, explaining the tiny ways lactoferrin works will help make new similar substances and small proteins with better strength.

Conclusion

Lactoferrin is a glycoprotein of great biochemical complexity, both structurally and with respect to its ability to bind iron, aspects central to its multifunctional biologically active properties. Its biochemical activities do not end at iron sequestration; enzymatic activities, receptor binding, and immunomodulation also come within their ambit. Its metabolism-that it is partially resistant to proteolysis and can generate active peptides- further augments its many physiological functions. Such biochemical and metabolic aspects are important in eliciting lactoferrin's therapeutic potential in many clinical applications. Indeed, new aspects of molecular mechanisms continue to be unveiled by research on lactoferrin as an important natural molecule involved in host defense as well as disease modulation. The clinical importance of lactoferrin is highlighted by its multiple roles in the regulation of infection and inflammation, cancer biology, neonatology, and systemic diseases. Proven as a diagnostic tool in the form of a biomarker and therapeutically as a natural immunomodulator and antimicrobial agent in many clinical scenarios. The challenges are numerous—but with continuous research and technological advances, applications for lactoferrin in precision medicine will broaden. With this understanding, lactoferrin will come to be included more integrally in upcoming plans for improved human health as well as disease intervention.

References

1. Actor, J. K., Hwang, S. A., & Kruzel, M. L. (2009). Lactoferrin as a natural immune modulator. *Current Pharmaceutical Design*, 15(17), 1956–1973. https://doi.org/10.2174/138161209788682325
2. Baker, E. N., & Baker, H. M. (2009). Molecular structure, binding properties and dynamics of lactoferrin. *Cellular and Molecular Life Sciences*, 66(1), 253–275. https://doi.org/10.1007/s00018-008-8412-1
3. Brock, J. H. (2012). Lactoferrin—50 years on. *Biochemistry and Cell Biology*, 90(3), 245–251. https://doi.org/10.1139/o2012-014
4. Brock, J. H. (2012). Lactoferrin—50 years on. *Biochemistry and Cell Biology*, 90(3), 245–251. https://doi.org/10.1139/o2012-014
5. Chang, R., Ng, T. B., & Sun, W. Z. (2020). Lactoferrin as potential preventive and adjunct treatment for COVID-19. *International Journal of Antimicrobial Agents*, 56(3), 106164. https://doi.org/10.1016/j.ijantimicag.2020.106164
6. Gibbons, J. A., Kozlowski, H., Hirschman, J., & Zimecki, M. (2015). Lactoferrin: The molecular balancing act of an immune modulator. *Nutrients*,

7(4), 2820–2838. https://doi.org/10.3390/nu7042820

7. Gifford, J. L., Hunter, H. N., & Vogel, H. J. (2005). Lactoferricin: a lactoferrin-derived peptide with antimicrobial, antiviral, antitumor and immunological properties. *Cellular and Molecular Life Sciences*, 62(22), 2588–2598. https://doi.org/10.1007/s00018-005-5414-2
8. Gisbert, J. P., & McNicholl, A. G. (2009). Questions and answers on the role of fecal biomarkers in inflammatory bowel disease. *Digestive Diseases and Sciences*, 54(6), 1177–1185. https://doi.org/10.1007/s10620-008-0456-4
9. González-Chávez, S. A., Arévalo-Gallegos, S., & Rascón-Cruz, Q. (2009). Lactoferrin: structure, function and applications. *International Journal of Antimicrobial Agents*, 33(4), 301.e1–301.e8. https://doi.org/10.1016/j.ijantimicag.2008.08.005
10. Huang, Y., et al. (2020). Antiviral properties of lactoferrin: A natural immune modulator. *Frontiers in Immunology*, 11, 2196. https://doi.org/10.3389/fimmu.2020.02196
11. Kao, D. W., Hsieh, Y. C., & Lin, Y. T. (2015). Clinical effects of lactoferrin on periodontal health: a systematic review. *Clinical Oral Investigations*, 19(7), 1645–1653. https://doi.org/10.1007/s00784-015-1450-1
12. Kruzel, M. L., Zimecki, M., & Actor, J. K. (2017). Lactoferrin in a context of inflammation-induced pathology. *Frontiers in Immunology*, 8, 1438. https://doi.org/10.3389/fimmu.2017.01438
13. Laursen, I., & Moestrup, S. K. (2009). Interactions of the transferrin family: receptors and ligands. *Cellular and Molecular Life Sciences*, 66(1), 103–116. https://doi.org/10.1007/s00018-008-8390-9
14. Legrand, D. (2016). Overview of lactoferrin as a natural immune modulator. *Journal of Pediatrics*, 173(Suppl), S10–S15. https://doi.org/10.1016/j.jpeds.2016.02.047
15. Legrand, D., Elass, E., Carpentier, M., & Mazurier, J. (2020). Lactoferrin: A modulator of immune and inflammatory responses. *Cellular and Molecular Life Sciences*, 77(2), 377–385. https://doi.org/10.1007/s00018-019-03329-4
16. Lönnerdal, B. (2009). Nutritional roles of lactoferrin. *Current Opinion in Clinical Nutrition and Metabolic Care*, 12(3), 293–297. https://doi.org/10.1097/MCO.0b013e32832929fc
17. Mäkitalo, L., Rautiainen, M., & Kolho, K.-L. (2016). Fecal lactoferrin: a noninvasive biomarker in inflammatory bowel disease. *World Journal of Gastroenterology*, 22(10), 2845–2851. https://doi.org/10.3748/wjg.v22.i10.2845
18. Manzoni, P., Rinaldi, M., Cattani, S., & Pugni, L. (2009). Oral supplementation with lactoferrin reduces the incidence of late-onset sepsis in very low birth weight neonates: a randomized trial. *The Journal of Pediatrics*, 155(5), 736–741. https://doi.org/10.1016/j.jpeds.2009.05.026
19. Nibbering, P. H. (2006). Lactoferrin and the innate mucosal immune defense. *Advances in Experimental Medicine and Biology*, 606, 53–63. https://doi.org/10.1007/978-0-387-34812-2_6
20. Ochoa, T. J., & Cleary, T. G. (2009). Effect of lactoferrin on enteric pathogens. *Biochimie*, 91(1), 30–34. https://doi.org/10.1016/j.biochi.2008.05.011
21. Pammi, M., & Suresh, G. (2017). Oral lactoferrin for the prevention of sepsis and necrotizing enterocolitis in preterm infants. *Cochrane Database of Systematic Reviews*, (6), CD007137. https://doi.org/10.1002/14651858.CD007137.pub4
22. Sánchez, L., Calvo, M., & Brock, J. H. (1992). Biological role of lactoferrin. *Archives of Disease in Childhood*, 67(5), 657–661. https://doi.org/10.1136/adc.67.5.657
23. Tian, Y., Zhang, Y., & Liu, H. (2015). Effects of lactoferrin on glycemic control and insulin resistance in diabetic rats. *Journal of Diabetes Research*, 2015, 1–9. https://doi.org/10.1155/2015/960892
24. Wakabayashi, H., Oda, H., & Yamauchi, K. (2014). Lactoferrin for prevention of common viral infections. *Journal of Infection and Chemotherapy*, 20(11), 666–671. https://doi.org/10.1016/j.jiac.2014.07.003
25. Ward, P. P., Paz, E., & Conneely, O. M. (2005). Multifunctional roles of lactoferrin: A critical overview. *Cellular and Molecular Life Sciences*, 62(22), 2540–2548. https://doi.org/10.1007/s00018-005-5372-1
26. Zhao, M., Liu, L., Chen, J., Zhang, C., & Wang, J. (2019). Advances in the delivery of lactoferrin for cancer therapy. *International Journal of Nanomedicine*, 14, 1183–1193. https://doi.org/10.2147/IJN.S190706