Lactoferrin - A Polyfunctional Protein and a Major Component of Colostrum

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Although first discovered in 1939, the molecule we now know as lactoferrin was not chemically purified and identified until 1960[1]. The term "lacto" in the name refers to the fact that it was originally identified in cow's milk and colostrum. Colostrum is particularly rich in lactoferrin where it makes up approximately 6% of the total protein, but lactoferrin is found in many bodily fluids, including tears, saliva, and other exocrine secretions as well as in neutrophil (white blood cell) granules.

Here it performs a vital function as a major portion of the innate immune system, a non-specific system that forms the initial layer of defense against all forms of pathogens - viral, bacterial, fungal, and even amebic[2]. But lactoferrin has many other functions in the body as well, including participation in iron homeostasis, anti-inflammatory and anti-tumor activity, analgesic activity, regulation of bone metabolism, reproductive functions, and regulation of embryonic development[3].

Lactoferrin's broad spectrum immune function is of primary interest. As part of the innate immune system, it defends against pathogens (disease-causing organisms) of all types. Its antiviral activity is particularly important as there are few pharmaceutical drugs which have proven at all effective against viruses. Lactoferrin has been shown to have antiviral activity against many viruses, including rotavirus (primary cause of diarrhea in young infants)[4], herpes simplex virus 1 and 2[5], canine herpes virus[6], feline herpes virus[7], echovirus[8], enterovirus[9], human papilloma virus (implicated in cervical and other human cancers)[10], polio virus[11], HIV and cytomegalovirus[12], Hepatitis B[13] and C[14] viruses, adenovirus[15], hanta virus[16], influenza virus[17], respiratory syncytial virus[18], Sindbis and Semliki Forest viruses (alphaviruses) [19].

Some of the mechanisms that lactoferrin employs against viruses include:

- Competes with viruses for binding sites on target cells[4-10]
- Binds directly to structural proteins of certain viruses, inactivating them[9].
- Interferes with hemagglutination (clumping of red blood cells) caused by influenza viruses[17].
- Inhibits certain viral enzymes required for viral replication[20-21]
- Exhibits synergy with a number of important antiviral drugs[22-24].
Lactoferrin also is very active against other pathogens, such as bacteria, fungi, and amebic parasites[25], while promoting the growth of beneficial bacteria, such as Lactobacilli and Bifidobacteria[26-27], to pass unharmed into the digestive tract.

- Lactoferrin prevents the colonization of Haemophilus influenzae, a major cause of ear and respiratory infections in children[28].
- Lactoferrin kills dangerous gram-negative bacteria, such as Vibrio cholerae, the cause of cholera, Salmonella, and E. coli[29] by attaching to and destroying the cell wall of the bacterium, allowing lysozyme to enter and lyse, or burst, the cell.
- Lactoferrin is very effective against fungal infections, such as Candida, through its iron-binding ability[30-31].

Lactoferrin also plays an important role in the immune system as an immunomodulator and growth stimulator.

- Lactoferrin increases the number and activity of T and B lymphocytes and Natural Killer (NK) cells[3].
- Lactoferrin modulates the release of a number of cytokines, including both pro- and anti-inflammatory[3].
- Lactoferrin promotes the maturation of T (both helper and suppressor) and B lymphocytes[32][33].
- Lactoferrin can mediate the response to Cytomegalovirus infection by T-lymphocyte augmentation of NK cell activity[34].
- Lactoferrin increases the cell-killing activity of NK cells and killer T-cells[35].
- Lactoferrin increases the activity of human polymorphonuclear leukocytes (white blood cells)[36].
- Lactoferrin is an essential growth factor for lymphocytes[37].

Similarly, lactoferrin has been shown to inhibit the manifestations of autoimmune disease, which involves down-regulation of the immune system.

- Lactoferrin controls the effector phase of the cellular immune response and inhibits the autoimmune response in mice[33].
- Lactoferrin lowers positive Coombs test results (a test for autoimmune blood disease) in mice[38].

In summary, lactoferrin is a multifaceted molecule which can significantly affect immune system performance and provide protection against viruses and other pathogens for which there are few if any effective treatments available.

[2] Ward, PP, Uribe-Luna S, Conneely, OM. Lactoferrin and host defense. *Biochemistry and Cell Biology* 80(1):95-102 (2002). Lactoferrin is a member of the nonheme iron-binding glycoproteins. It is found predominantly on mucosal surfaces where it functions as a prominent component of the first line of host defense against inflammation and infection. It is also found in the granules of neutrophils. It has a host of other functions as well.

[3] Artym, J. Antitumor and chemopreventive activity of lactoferrin] *Postępy Higieny i Medycyny Doświadczalnej* 60:352-369 (2006). Lactoferrin participates in iron homeostasis, has immunoregulatory, anti-inflammatory, anti-tumor, and analgesic actions, regulation of bone metabolism, participates in embryonic development, reproductive functions, and others. It provides anti-tumor protection through its immunomodulatory abilities, so it is of particular value in cancer patients with impaired immunity. Lactoferrin increases the number and the activity of T and B cells and NK cells, stimulates the release of a number of cytokines (IL-1, IL-6, IL-8, IL-18, IFN-γ, TNF-α), increases the phagocytic and cytotoxic activity of monocytes and macrophages, accelerates the maturation of T and B cells, and elevates the expression of several types of cellular receptors, including CD4, zeta chain of the CD3 complex, LFA-1, CD11, ICAM-1, and selectin P. In addition, it also exhibits chemopreventive properties, regulates the activity of Phase I and Phase II enzymes which participate in the activation and detoxification of carcinogens, and regulates the composition of the intestinal flora.


[9] Weng, TY, Chen, LC, Shyu, HW, Chen, SH, Wang, JR, Yu, CK, Lei, HY, Yeh, TM. Lactoferrin inhibits enterovirus 71 infection by binding to VP1 protein and host cells. *Antiviral Research* 67(1):31-37 (2005). Lactoferrin binds to host cells, preventing enterovirus 71 from attaching to them. It also interferes with the virus by binding to its VP1 protein.


[18] van der Strate, BW, et al. **Antiviral activities of lactoferrin.** *Antiviral Research* 52(3):225-239 (2001). Lactoferrin is effective against both DNA and RNA viruses, including rotavirus, respiratory
syncytial virus, herpes virus and HIV, both by blocking cellular receptors and by directly binding to the viruses.


[23] van der Strate, BW, De Boer, FM, Bakker, HI, Meijer, DK, Molema, G, Harmsen, MC. Synergy of bovine lactoferrin with the anti-cytomegalovirus drug cidofovir in vitro. *Antiviral Research* 58(2):159-165 (2003). Combining lactoferrin with acyclovir or foscarnet resulted in antagonism, lactoferrin and ganciclovir showed neither antagonism or synergy, but lactoferrin with cidofovir showed marked synergy against cytomegalovirus.

[24] Andersen, JH, Jenssen, H, Gutteberg, TJ. Lactoferrin and lactoferricin inhibit Herpes simplex 1 and 2 infection and exhibit synergy when combined with acyclovir. *Antiviral Research* 58(3):209-215 (2003). When used against HSV-1 and -2, the combination of lactoferrin or its peptide lactoferricin with acyclovir demonstrated good synergy. The effective dosage of both lactoferrin and acyclovir could be reduced 2-7 times.
[25] van Hooijdonk, AC, Kussendrager, KD, Steijns, JM. In vivo antimicrobial and antiviral activity of components in bovine milk and colostrum involved in non-specific defense. *British Journal of Nutrition* 84(Suppl.1):S127-S134 (2000). Lactoferrin and lactoperoxidase, both present in colostrum in large amounts, provide non-specific defense against a broad spectrum of pathogens, including bacteria and viruses. This is significant both for the protection of commercially important animals as well as humans.


[29] Ellison, RT III, Giehl, TJ. Killing of gram-negative bacteria by lactoferrin and lysozyme. *Journal of Clinical Investigation* 88(4):1080-1091 (1991). Lactoferrin and lysozyme act together to kill gram-negative bacteria, such as *Vibrio cholerae* (cholera), *Salmonella typhimurium* (food poisoning) and *Eschericia coli*. The lactoferrin attaches to and destroys the cell wall of the bacteria, allowing the lysozyme to enter and lyse (burst) the organisms.


lysozyme is very effective in killing nearly all oral strains of Candida, which is of particular importance to AIDS sufferers who are often unable to fight off Candida overgrowths, such as thrush.


[33] Adamik, B, Wlaszczyk, A. [Lactoferrin - its role in defense against infection and immunotropic properties] *Postęp Higieny i Medycyny Doświadczalnej* 50(1):33-41 (1996). Lactoferrin (LF) is an iron-binding protein found in milk and other secretory fluids of mammals as well as in secondary granules of neutrophils. Receptors for LF were detected and isolated on activated T and B cells, monocytes, intestinal brush border cells, platelets and neoplastic cells. Very low physiologic serum levels of LF increase significantly upon infection. Serum concentration of LF is also elevated in rheumatoid patients. It is suggested that the ability of LF to bind an excess of Fe(II) ions, needed for growth of microorganisms and tumors, represents an important defence mechanism in humans. LF, in addition, may contribute to the protection against pathogens and their metabolites by enhancing phagocytosis, cell adherence and controlling release of proinflammatory cytokines such as IL-1, IL-6 and TNF-alpha. The protein also diminishes the damaging effects of free radical release. LF possesses interesting immunotropic properties with regard to immature T and B cells by promoting phenotypic and functional maturation of these cells. LF also controls the effector phase of cellular immune response and inhibits manifestations of autoimmune response in mice.

[34] Shimizu,K, et al. Lactoferrin-mediated protection of the host from murine cytomegalovirus infection by a T-cell-dependent augmentation of natural killer cell activity. *Archives of Virology* 141(10):1875-89 (1996). Administering bovine Lactoferrin prior to Cytomegalovirus infection completely protected infected mice from dying from the infection. This was accompanied by a concomitant increase in NK cell activity, which was shown to be a result of T-cell interaction with the NK cells.


[37] Hashizume, S, et al. **Identification of lactoferrin as an essential growth factor for human lymphocytic cell lines in serum-free medium.** *Biochimica et Biophysica Acta* 763(4):377-382 (1983). Lactoferrin is an essential growth factor for lymphocytes. It has higher growth stimulatory activity than transferrin. Bovine lactoferrin was found to be as effective as human.

[38] Zimecki, M, et al. **Lactoferrin lowers the incidence of positive Coombs' test in New Zealand black mice.** *Archivum Immunologiae et Therapiae Experimentalis* 43(3-4):207-9 (1995). Prolonged treatment with bovine lactoferrin of New Zealand Black mice shows a decreased frequency of positive Coombs' test. These data indicate that lactoferrin may be of therapeutic value in the treatment of autoimmune disorders.

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