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

Références

- Adams WC, Bond E, Havenga MJ, Holterman L, Goudsmit J, Karlsson Hedestam GB, et al.. 2009. Adenovirus serotype 5 infects human dendritic cells via a coxsackievirus-adenovirus receptor-independent receptor pathway mediated by lactoferrin and DC-SIGN. J. Gen. Virol. **90**(7): 1600-1610 CrossRef, Medline.
- Afeltra A, Caccavo D, Ferri GM, Addessi MA, De Rosa FG, Amoroso A, Bonomo L. 1997. Expression of lactoferrin on human granulocytes: analysis with polyclonal and monoclonal antibodies. Clin. Exp. Immunol. **109**(2): 279-285 CrossRef, Medline.
- Akira S, Hemmi H. 2003. Recognition of pathogen-associated molecular patterns by TLR family. Immunol. Lett. **85**(2): 85-95 CrossRef, Medline.
- Ando K, Hasegawa K, Shindo K, Furusawa T, Fujino T, Kikugawa K, et al.. 2010. Human lactoferrin activates NF-κB through the Toll-like receptor 4 pathway while it interferes with the lipopolysaccharide-stimulated TLR4 signaling. FEBS J. **277**(9): 2051-2066 CrossRef, Medline.
- Annane D, Bellissant E, Cavaillon JM. 2005. Septic shock. Lancet **365**(9453): 63-78 CrossRef,Medline.
- Appelmelk BJ, An YQ, Geerts M, Thijs BG, de Boer HA, MacLaren DM, et al.. 1994. Lactoferrin is a lipid A-binding protein. Infect. Immun. **62**(6): 2628-2632 Medline.

- Artym J, Zimecki M, Kruzel ML. 2003. Reconstitution of the cellular immune response by lactoferrin in cyclophosphamide-treated mice is correlated with renewal of T cell compartment. Immunobiology**207**(3): 197-205 CrossRef, Medline.
- Artym J, Zimecki M, Kruzel ML. 2004. Effects of lactoferrin on IL-6 production by peritoneal and alveolar cells in cyclophosphamide-treated mice. J. Chemother. **16**(2): 187-192 Medline.
- Baker EN, Baker HM. 2005. Molecular structure, binding properties and dynamics of lactoferrin. Cell. Mol. Life Sci. **62**(22): 2531-2539 CrossRef, Medline.
- Baveye S, Elass E, Mazurier J, Legrand D. 2000*a*. Lactoferrin inhibits the binding of lipopolysaccharides to L-selectin and subsequent production of reactive oxygen species by neutrophils. FEBS Lett. **469**(1): 5-8 CrossRef, Medline.
- Baveye S, Elass E, Fernig DG, Blanquart C, Mazurier J, Legrand D. 2000*b*. Human lactoferrin interacts with soluble CD14 and inhibits expression of endothelial adhesion molecules, E-selectin and ICAM-1, induced by the CD14-lipopolysaccharide complex. Infect. Immun. **68**(12): 6519-6525CrossRef, Medline.
- Bennett RM, Kokocinski T. 1978. Lactoferrin content of peripheral blood cells. Br. J. Haematol. **39**(4): 509-521 CrossRef, Medline.
- Bi BY, Liu JL, Legrand D, Roche AC, Capron M, Spik G, Mazurier J. 1996. Internalization of human lactoferrin by the Jurkat human lymphoblastic T-cell line. Eur. J. Cell Biol. **69**(3): 288-296 Medline.
- Birgens HS, Kristensen LO, Borregaard N, Karle H, Hansen NE. 1988. Lactoferrin-mediated transfer of iron to intracellular ferritin in human monocytes. Eur. J. Haematol. **41**(1): 52-57 CrossRef,Medline.
- Borghesi LA, Yamashita Y, Kincade PW. 1999. Heparan sulfate proteoglycans mediate interleukin-7-dependent B lymphopoiesis. Blood **93**(1): 140-148 Medline.
- Bournazou I, Pound JD, Duffin R, Bournazos S, Melville LA, Brown SB, et al.. 2009. Apoptotic human cells inhibit migration of granulocytes via release of lactoferrin. J. Clin. Invest. **119**(1): 20-32Medline.
- Bournazou I, Mackenzie KJ, Duffin R, Rossi AG, Gregory CD. 2010. Inhibition of eosinophil migration by lactoferrin. Immunol. Cell Biol. **88**(2): 220-223 CrossRef, Medline.
- Brandenburg K, Jurgens G, Muller M, Fukuoka S, Koch MH. 2001. Biophysical characterization of lipopolysaccharide and lipid A inactivation by lactoferrin. Biol. Chem. **382**(8): 1215-1225 CrossRef,Medline.
- Breton-Gorius J, Mason DY, Buriot D, Vilde JL, Griscelli C. 1980. Lactoferrin deficiency as a consequence of a lack of specific granules in neutrophils from a patient with recurrent infections. Detection by immunoperoxidase staining for lactoferrin and cytochemical electron microscopy. Am. J. Pathol. **99**(2): 413-428 Medline.
- Britigan BE, Serody JS, Hayek MB, Charniga LM, Cohen MS. 1991. Uptake of lactoferrin by mononuclear phagocytes inhibits their ability to form hydroxyl radical and protects them from membrane autoperoxidation. J. Immunol. **147**(12): 4271-4277 Medline.
- Britigan BE, Lewis TS, Waldschmidt M, McCormick ML, Krieg AM. 2001. Lactoferrin binds CpG-containing oligonucleotides and inhibits their immunostimulatory effects on human B cells. J. Immunol. **167**(5): 2921-2928 Medline.
- Broxmeyer HE, Williams DE, Hangoc G, Cooper S, Gentile P, Shen RN, et al.. 1987. The opposing actions in vivo on murine myelopoiesis of purified preparations of lactoferrin and the colony stimulating factors. Blood Cells **13**(1–2): 31-48 Medline.
- Buderus S, Boone J, Lyerly D, Lentze MJ. 2004. Fecal lactoferrin: a new parameter to monitor infliximab therapy. Dig. Dis. Sci. **49**(6): 1036-1039 CrossRef, Medline.
- Caccavo D, Sebastiani GD, Di Monaco C, Guido F, Galeazzi M, Ferri GM, et al.. 1999. Increased levels of lactoferrin in synovial fluid but not in serum from patients with rheumatoid arthritis. Int. J. Clin. Lab. Res. **29**(1): 30-35 CrossRef, Medline.
- Chodaczek G, Zimecki M, Lukasiewicz J, Lugowski C. 2006. A complex of lactoferrin with monophosphoryl lipid A is an efficient adjuvant of the humoral and cellular immune response in mice. Med. Microbiol. Immunol. (Berl.) **195**(4): 207-216 CrossRef, Medline.
- Chodaczek G, Zimecki M, Lukasiewicz J, Lugowski C. 2008. Lactoferrin-monophosphoryl lipid A complex enhances immunity of mice to *Plesiomonas shigelloides* CNCTC 138/92. Acta Biochim. Pol. **55**(1): 91-96 Medline.

- Crouch SP, Slater KJ, Fletcher J. 1992. Regulation of cytokine release from mononuclear cells by the iron-binding protein lactoferrin. Blood **80**(1): 235-240 Medline.
- Cumberbatch M, Bhushan M, Dearman RJ, Kimber I, Griffiths CE. 2003. IL-1β-induced Langerhans' cell migration and TNF-α production in human skin: regulation by lactoferrin. Clin. Exp. Immunol.**132**(2): 352-359 CrossRef, Medline.
- Curran CS, Demick KP, Mansfield JM. 2006. Lactoferrin activates macrophages via TLR4-dependent and -independent signaling pathways. Cell. Immunol. **242**(1): 23-30 CrossRef, Medline.
- Damiens E, El Yazidi I, Mazurier J, Elass-Rochard E, Duthille I, Spik G, Boilly-Marer Y. 1998. Role of heparan sulphate proteoglycans in the regulation of human lactoferrin binding and activity in the MDA-MB-231 breast cancer cell line. Eur. J. Cell Biol. **77**(4): 344-351 Medline.
- de la Rosa G, Yang D, Tewary P, Varadhachary A, Oppenheim JJ. 2008. Lactoferrin acts as an alarmin to promote the recruitment and activation of APCs and antigen-specific immune responses. J. Immunol. **180**(10): 6868-6876 Medline.
- Debanne MT, Regoeczi E, Sweeney GD, Krestynski F. 1985. Interaction of human lactoferrin with the rat liver. Am. J. Physiol. **248**(4 Pt 1): G463-G469 Medline.
- Debbabi H, Dubarry M, Rautureau M, Tome D. 1998. Bovine lactoferrin induces both mucosal and systemic immune response in mice. J. Dairy Res. **65**(2): 283-293 CrossRef, Medline.
- Delehedde M, Lyon M, Sergeant N, Rahmoune H, Fernig DG. 2001. Proteoglycans: pericellular and cell surface multireceptors that integrate external stimuli in the mammary gland. J. Mammary Gland Biol. Neoplasia **6**(3): 253-273 CrossRef, Medline.
- Deriy LV, Chor J, Thomas LL. 2000. Surface expression of lactoferrin by resting neutrophils. Biochem. Biophys. Res. Commun. **275**(1): 241-246 CrossRef, Medline.
- Dhennin-Duthille I, Masson M, Damiens E, Fillebeen C, Spik G, Mazurier J. 2000. Lactoferrin upregulates the expression of CD4 antigen through the stimulation of the mitogen-activated protein kinase in the human lymphoblastic T Jurkat cell line. J. Cell. Biochem. **79**(4): 583-593 CrossRef,Medline.
- Dial EJ, Dohrman AJ, Romero JJ, Lichtenberger LM. 2005. Recombinant human lactoferrin prevents NSAID-induced intestinal bleeding in rodents. J. Pharm. Pharmacol. **57**(1): 93-99CrossRef, Medline.
- Elass E, Masson M, Mazurier J, Legrand D. 2002. Lactoferrin inhibits the lipopolysaccharide-induced expression and proteoglycan-binding ability of interleukin-8 in human endothelial cells. Infect. Immun. **70**(4): 1860-1866 CrossRef, Medline.
- Elass-Rochard E, Roseanu A, Legrand D, Trif M, Salmon V, Motas C, et al.. 1995. Lactoferrin-lipopolysaccharide interaction: involvement of the 28-34 loop region of human lactoferrin in the high-affinity binding to *Escherichia coli* 055B5 lipopolysaccharide. Biochem. J. **312**(Pt 3): 839-845Medline.
- Elass-Rochard E, Legrand D, Salmon V, Roseanu A, Trif M, Tobias PS, et al.. 1998. Lactoferrin inhibits the endotoxin interaction with CD14 by competition with the lipopolysaccharide-binding protein. Infect. Immun. **66**(2): 486-491 Medline.
- Elrod KC, Moore WR, Abraham WM, Tanaka RD. 1997. Lactoferrin, a potent tryptase inhibitor, abolishes late-phase airway responses in allergic sheep. Am. J. Respir. Crit. Care Med. **156**(2 Pt 1): 375-381 Medline.
- Fillebeen C, Mitchell V, Dexter D, Benaissa M, Beauvillain J, Spik G, Pierce A. 1999*a*. Lactoferrin is synthesized by mouse brain tissue and its expression is enhanced after MPTP treatment. Brain Res. Mol. Brain Res. **72**(2): 183-194 CrossRef, Medline.
- Fillebeen C, Descamps L, Dehouck MP, Fenart L, Benaissa M, Spik G, et al.. 1999*b*. Receptor-mediated transcytosis of lactoferrin through the blood–brain barrier. J. Biol. Chem. **274**(11): 7011-7017 CrossRef, Medline.
- Fischer R, Debbabi H, Dubarry M, Boyaka P, Tome D. 2006. Regulation of physiological and pathological Th1 and Th2 responses by lactoferrin. Biochem. Cell Biol. **84**(3): 303-311 Lien, ISI.Abstract
- Fischer R, Debbabi H, Blais A, Dubarry M, Rautureau M, Boyaka PN, Tome D. 2007. Uptake of ingested bovine lactoferrin and its accumulation in adult mouse tissues. Int. Immunopharmacol.**7**(10): 1387-1393 CrossRef, Medline.
- Frydecka I, Zimecki M, Bocko D, Kosmaczewska A, Teodorowska R, Ciszak L, et al.. 2002. Lactoferrin-induced up-regulation of zeta (zeta) chain expression in peripheral blood T lymphocytes from cervical cancer patients. Anticancer Res. **22**(3): 1897-1901 Medline.

- Gahr M, Speer CP, Damerau B, Sawatzki G. 1991. Influence of lactoferrin on the function of human polymorphonuclear leukocytes and monocytes. J. Leukoc. Biol. **49**(5): 427-433 Medline.
- Gliemann J. 1998. Receptors of the low density lipoprotein (LDL) receptor family in man. Multiple functions of the large family members via interaction with complex ligands. Biol. Chem. **379**(8–9): 951-964 Medline.
- Graham SA, Antonopoulos A, Hitchen PG, Haslam SM, Dell A, Drickamer K, Taylor ME. 2011. Identification of neutrophil granule glycoproteins as Lewis(x)-containing ligands cleared by the scavenger receptor C-type lectin. J. Biol. Chem. **286**(27): 24336-24349 CrossRef, Medline.
- Greenberg DE, Jiang ZD, Steffen R, Verenker MP, DuPont HL. 2002. Markers of inflammation in bacterial diarrhea among travelers, with a focus on enteroaggregative *Escherichia coli*pathogenicity. J. Infect. Dis. **185**(7): 944-949 CrossRef, Medline.
- Grey A, Banovic T, Zhu Q, Watson M, Callon K, Palmano K, et al.. 2004. The low-density lipoprotein receptor-related protein 1 is a mitogenic receptor for lactoferrin in osteoblastic cells. Mol. Endocrinol. **18**(9): 2268-2278 CrossRef, Medline.
- Griffiths CE, Cumberbatch M, Tucker SC, Dearman RJ, Andrew S, Headon DR, Kimber I. 2001. Exogenous topical lactoferrin inhibits allergen-induced Langerhans cell migration and cutaneous inflammation in humans. Br. J. Dermatol. **144**(4): 715-725 CrossRef, Medline.
- Groot F, Geijtenbeek TB, Sanders RW, Baldwin CE, Sanchez-Hernandez M, Floris R, et al.. 2005. Lactoferrin prevents dendritic cell-mediated human immunodeficiency virus type 1 transmission by blocking the DC-SIGN–gp120 interaction. J. Virol. **79**(5): 3009-3015 CrossRef, Medline.
- Guillén C, McInnes IB, Vaughan D, Speekenbrink AB, Brock JH. 2000. The effects of local administration of lactoferrin on inflammation in murine autoimmune and infectious arthritis. Arthritis Rheum. **43**(9): 2073-2080 CrossRef, Medline.
- Guillén C, McInnes IB, Vaughan DM, Kommajosyula S, Van Berkel PH, Leung BP, et al.. 2002. Enhanced Th1 response to *Staphylococcus aureus* infection in human lactoferrin-transgenic mice. J. Immunol. **168**(8): 3950-3957 Medline.
- Håversen L, Ohlsson BG, Hahn-Zoric M, Hanson LÅ, Mattsby-Baltzer I. 2002. Lactoferrin down-regulates the LPS-induced cytokine production in monocytic cells via NF-κ B. Cell. Immunol. **220**(2): 83-95 CrossRef, Medline.
- Hayashida K, Kaneko T, Takeuchi T, Shimizu H, Ando K, Harada E. 2004. Oral administration of lactoferrin inhibits inflammation and nociception in rat adjuvant-induced arthritis. J. Vet. Med. Sci.**66**(2): 149-154 CrossRef, Medline.
- Hayworth JL, Kasper KJ, Leon-Ponte M, Herfst CA, Yue D, Brintnell WC, et al.. 2009. Attenuation of massive cytokine response to the staphylococcal enterotoxin B superantigen by the innate immunomodulatory protein lactoferrin. Clin. Exp. Immunol. **157**(1): 60-70 CrossRef, Medline.
- He J, Furmanski P. 1995. Sequence specificity and transcriptional activation in the binding of lactoferrin to DNA. Nature **373**(6516): 721-724 CrossRef, Medline.
- He SH, Xie H. 2004. Modulation of histamine release from human colon mast cells by protease inhibitors. World J. Gastroenterol. **10**(3): 337-341 Medline.
- He S, McEuen AR, Blewett SA, Li P, Buckley MG, Leufkens P, Walls AF. 2003. The inhibition of mast cell activation by neutrophil lactoferrin: uptake by mast cells and interaction with tryptase, chymase and cathepsin G. Biochem. Pharmacol. **65**(6): 1007-1015 CrossRef, Medline.
- Herz J, Strickland DK. 2001. LRP: a multifunctional scavenger and signaling receptor. J. Clin. Invest.**108**(6): 779-784 CrossRef, Medline.
- Hwang S-A, Actor JK. 2009. Lactoferrin modulation of BCG-infected dendritic cell functions. Int. Immunol. **21**(10): 1185-1197 CrossRef, Medline.
- Hwang S-A, Kruzel ML, Actor JK. 2005. Lactoferrin augments BCG vaccine efficacy to generate T helper response and subsequent protection against challenge with virulent *Mycobacterium tuberculosis*. Int. Immunopharmacol. **5**(3): 591-599 CrossRef, Medline.
- Hwang S-A, Kruzel ML, Actor JK. 2009. Influence of bovine lactoferrin on expression of presentation molecules on BCG-infected bone marrow derived macrophages. Biochimie **91**(1): 76-85 CrossRef,Medline.

- Iigo M, Shimamura M, Matsuda E, Fujita K, Nomoto H, Satoh J, et al.. 2004. Orally administered bovine lactoferrin induces caspase-1 and interleukin-18 in the mouse intestinal mucosa: a possible explanation for inhibition of carcinogenesis and metastasis. Cytokine **25**(1): 36-44 CrossRef,Medline.
- Ishii K, Takamura N, Shinohara M, Wakui N, Shin H, Sumino Y, et al.. 2003. Long-term follow-up of chronic hepatitis C patients treated with oral lactoferrin for 12 months. Hepatol. Res. **25**(3): 226-233CrossRef, Medline.
- Ismail M, Brock JH. 1993. Binding of lactoferrin and transferrin to the human promonocytic cell line U937. Effect on iron uptake and release. J. Biol. Chem. **268**(29): 21618-21625 Medline.
- Jenssen H, Hancock RE. 2009. Antimicrobial properties of lactoferrin. Biochimie **91**(1): 19-29CrossRef, Medline.
- Jerala R. 2007. Structural biology of the LPS recognition. Int. J. Med. Microbiol. **297**(5): 353-363CrossRef, Medline.
- Judd TA, Day AS, Lemberg DA, Turner D, Leach ST. 2011. Update of fecal markers of inflammation in inflammatory bowel disease. J. Gastroenterol. Hepatol. **26**(10): 1493-1499 CrossRef, Medline.
- Kai K, Komine K, Komine Y, Kuroishi T, Kozutsumi T, Kobayashi J, et al.. 2002. Lactoferrin stimulates A *Staphylococcus aureus* killing activity of bovine phagocytes in the mammary gland. Microbiol. Immunol. **46**(3): 187-194 Medline.
- Kallenberg CGM, Mulder AHL, Tervaert JWC. 1992. Antineutrophil cytoplasmic antibodies: a still-growing class of autoantibodies in inflammatory disorders. Am. J. Med. **93**(6): 675-682 CrossRef,Medline.
- Kane SV, Sandborn WJ, Rufo PA, Zholudev A, Boone J, Lyerly D, et al.. 2003. Fecal lactoferrin is a sensitive and specific marker in identifying intestinal inflammation. Am. J. Gastroenterol. **98**(6): 1309-1314 CrossRef, Medline.
- Kijlstra A, Jeurissen SH. 1982. Modulation of classical C3 convertase of complement by tear lactoferrin. Immunology **47**(2): 263-270 Medline.
- Kimber I, Cumberbatch M, Dearman RJ, Headon DR, Bhushan M, Griffiths CE. 2002. Lactoferrin: influences on Langerhans cells, epidermal cytokines, and cutaneous inflammation. Biochem. Cell Biol. **80**(1): 103-107 Lien, ISI. Abstract
- Kobayashi S, Abe Y, Inanami O, Oda S, Yamauchi K, Hankanga C, et al.. 2011. Oral administration of bovine lactoferrin upregulates neutrophil functions in a dog with familial β2-integrin-related neutrophil dysfunction. Vet. Immunol. Immunopathol. **143**(1–2): 155-161 CrossRef, Medline.
- Konishi M, Iwasa M, Yamauchi K, Sugimoto R, Fujita N, Kobayashi Y, et al.. 2006. Lactoferrin inhibits lipid peroxidation in patients with chronic hepatitis C. Hepatol. Res. **36**(1): 27-32 CrossRef, Medline.
- Kruzel ML, Harari Y, Mailman D, Actor JK, Zimecki M. 2002. Differential effects of prophylactic, concurrent and therapeutic lactoferrin treatment on LPS-induced inflammatory responses in mice. Clin. Exp. Immunol. **130**(1): 25-31 CrossRef, Medline.
- Kruzel ML, Bacsi A, Choudhury B, Sur S, Boldogh I. 2006. Lactoferrin decreases pollen antigen-induced allergic airway inflammation in a murine model of asthma. Immunology **119**(2): 159-166CrossRef, Medline.
- Kruzel ML, Actor JK, Radak Z, Bacsi A, Saavedra-Molina A, Boldogh I. 2010. Lactoferrin decreases LPS-induced mitochondrial dysfunction in cultured cells and in animal endotoxemia model. Innate Immun. **16**(2): 67-79 CrossRef, Medline.
- Kuhara T, Iigo M, Itoh T, Ushida Y, Sekine K, Terada N, et al.. 2000. Orally administered lactoferrin exerts an antimetastatic effect and enhances production of IL-18 in the intestinal epithelium. Nutr. Cancer **38**(2): 192-199 CrossRef, Medline.
- Kuhara T, Yamauchi K, Tamura Y, Okamura H. 2006. Oral administration of lactoferrin increases NK cell activity in mice via increased production of IL-18 and type I IFN in the small intestine. J. Interferon Cytokine Res. **26**(7): 489-499 CrossRef, Medline.
- Kuhara T, Yamauchi K, Iwatsuki K. 2011. Bovine lactoferrin induces interleukin-11 production in a hepatitis mouse model and human intestinal myofibroblasts. Eur. J. Nutr. In press CrossRef
- Kurose I, Yamada T, Wolf R, Granger DN. 1994. P-selectin-dependent leukocyte recruitment and intestinal mucosal injury induced by lactoferrin. J. Leukoc. Biol. **55**(6): 771-777 Medline.

- Larsen A, Hovdenak N, Karlsdottir A, Wentzel-Larsen T, Dahl O, Fagerhol MK. 2004. Faecal calprotectin and lactoferrin as markers of acute radiation proctitis: a pilot study of eight stool markers. Scand. J. Gastroenterol. **39**(11): 1113-1118 CrossRef, Medline.
- Lee WJ, Farmer JL, Hilty M, Kim YB. 1998. The protective effects of lactoferrin feeding against endotoxin lethal shock in germfree piglets. Infect. Immun. **66**(4): 1421-1426 Medline.
- Legrand D, Mazurier J. 2010. A critical review of the roles of host lactoferrin in immunity. Biometals**23**(3): 365-376 CrossRef, Medline.
- Legrand D, van Berkel PH, Salmon V, van Veen HA, Slomianny MC, Nuijens JH, Spik G. 1997. The N-terminal Arg2, Arg3 and Arg4 of human lactoferrin interact with sulphated molecules but not with the receptor present on Jurkat human lymphoblastic T-cells. Biochem. J. **327**(3): 841-846 Medline.
- Legrand D, Vigie K, Said EA, Elass E, Masson M, Slomianny MC, et al.. 2004. Surface nucleolin participates in both the binding and endocytosis of lactoferrin in target cells. Eur. J. Biochem. **271**(2): 303-317 CrossRef, Medline.
- Legrand D, Elass E, Carpentier M, Mazurier J. 2006. Interactions of lactoferrin with cells involved in immune function. Biochem. Cell Biol. **84**(3): 282-290 Lien, ISI. Abstract
- Legrand D, Pierce A, Elass E, Carpentier M, Mariller C, Mazurier J. 2008. Lactoferrin structure and functions. Adv. Exp. Med. Biol. **606**: 163-194 CrossRef, Medline.
- Leveugle B, Mazurier J, Legrand D, Mazurier C, Montreuil J, Spik G. 1993. Lactotransferrin binding to its platelet receptor inhibits platelet aggregation. Eur. J. Biochem. **213**(3): 1205-1211 CrossRef,Medline.
- Lobie PE, Mertani H, Morel G, Morales-Bustos O, Norstedt G, Waters MJ. 1994. Receptor-mediated nuclear translocation of growth hormone. J. Biol. Chem. **269**(33): 21330-21339 Medline.
- Lönnerdal B. 2009. Nutritional roles of lactoferrin. Curr. Opin. Clin. Nutr. Metab. Care **12**(3): 293-297CrossRef, Medline.
- Losfeld M-E, Khoury DE, Mariot P, Carpentier M, Krust B, Briand J-P, et al.. 2009. The cell surface expressed nucleolin is a glycoprotein that triggers calcium entry into mammalian cells. Exp. Cell Res. **315**(2): 357-369 CrossRef, Medline.
- Losfeld M-E, Leroy A, Coddeville B, Carpentier M, Mazurier J, Legrand D. 2011. N-glycosylation influences the structure and self-association abilities of recombinant nucleolin. FEBS J. **278**(14): 2552-2564 CrossRef, Medline.
- Maacks S, Yuan H-Z, Wood WG. 1989. Development and evaluation of luminescence-based sandwich assay for plasma lactoferrin as a marker for sepsis and bacterial infections in pediatric medicine. J. Biolumines. Chemilumines. **3**(4): 221-226 CrossRef.
- Machnicki M, Zimecki M, Zagulski T. 1993. Lactoferrin regulates the release of tumour necrosis factor alpha and interleukin 6 in vivo. Int. J. Exp. Pathol. **74**(5): 433-439 Medline.
- Malet A, Bournaud E, Lan A, Mikogami T, Tome D, Blais A. 2011. Bovine lactoferrin improves bone status of ovariectomized mice via immune function modulation. Bone **48**(5): 1028-1035 CrossRef,Medline.
- Maneva AI, Sirakov LM, Manev VV. 1983. Lactoferrin binding to neutrophilic polymorphonuclear leucocytes. Int. J. Biochem. **15**(7): 981-984 CrossRef, Medline.
- Mann DM, Romm E, Migliorini M. 1994. Delineation of the glycosaminoglycan-binding site in the human inflammatory response protein lactoferrin. J. Biol. Chem. **269**(38): 23661-23667 Medline.
- Masson PL, Heremans JF, Schonne E. 1969. Lactoferrin, an iron-binding protein in neutrophilic leukocytes. J. Exp. Med. **130**(3): 643-658 CrossRef, Medline.
- Mattsby-Baltzer I, Roseanu A, Motas C, Elverfors J, Engberg I, Hanson LA. 1996. Lactoferrin or a fragment thereof inhibits the endotoxin-induced interleukin-6 response in human monocytic cells. Pediatr. Res. **40**(2): 257-262 CrossRef, Medline.
- Mazurier J, Lhoste JM, Montreuil J, Spik G. 1983. Comparative study of the iron-binding properties of human transferrins. II. Electron paramagnetic resonance of mixed metal complexes of human lactotransferrin. Biochim. Biophys. Acta **745**(1): 44-49 CrossRef, Medline.

- Mazurier J, Legrand D, Hu WL, Montreuil J, Spik G. 1989. Expression of human lactotransferrin receptors in phytohemagglutinin-stimulated human peripheral blood lymphocytes. Isolation of the receptors by antiligand-affinity chromatography. Eur. J. Biochem. **179**(2): 481-487 CrossRef,Medline.
- McAbee DD, Jiang X, Walsh KB. 2000. Lactoferrin binding to the rat asialoglycoprotein receptor requires the receptor's lectin properties. Biochem. J. **348**(1): 113-117 CrossRef, Medline.
- Meilinger M, Haumer M, Szakmary KA, Steinbock F, Scheiber B, Goldenberg H, Huettinger M. 1995. Removal of lactoferrin from plasma is mediated by binding to low density lipoprotein receptor-related protein/α 2-macroglobulin receptor and transport to endosomes. FEBS Lett. **360**(1): 70-74CrossRef, Medline.
- Miller JD, Stevens ET, Smith DR, Wight TN, Wrenshall LE. 2008. Perlecan: a major IL-2-binding proteoglycan in murine spleen. Immunol. Cell Biol. **86**(2): 192-199 CrossRef, Medline.
- Miyauchi H, Hashimoto S, Nakajima M, Shinoda I, Fukuwatari Y, Hayasawa H. 1998. Bovine lactoferrin stimulates the phagocytic activity of human neutrophils: identification of its active domain. Cell. Immunol. **187**(1): 34-37 CrossRef, Medline.
- Miyazawa K, Mantel C, Lu L, Morrison DC, Broxmeyer HE. 1991. Lactoferrin-lipopolysaccharide interactions. Effect on lactoferrin binding to monocyte/macrophage-differentiated HL-60 cells. J. Immunol. **146**(2): 723-729 Medline.
- Montreuil J, Tonnelat J, Mullet S. 1960. [Preparation and properties of lactosiderophilin (lactotransferrin) of human milk.] Biochim. Biophys. Acta **45**: 413-421 CrossRef, Medline.
- Mukaida N. 2000. Interleukin-8 : an expanding universe beyond neutrophil chemotaxis and activation. Int. J. Hematol. **72**(4): 391-398 Medline.
- Muramatsu T, Muramatsu H. 2008. Glycosaminoglycan-binding cytokines as tumor markers. Proteomics **8**(16): 3350-3359 CrossRef, Medline.
- Na YJ, Han SB, Kang JS, Yoon YD, Park SK, Kim HM, et al.. 2004. Lactoferrin works as a new LPS-binding protein in inflammatory activation of macrophages. Int. Immunopharmacol. **4**(9): 1187-1199CrossRef, Medline.
- Nielsen SM, Hansen GH, Danielsen EM. 2010. Lactoferrin targets T cells in the small intestine. J. Gastroenterol. **45**(11): 1121-1128 CrossRef, Medline.
- Ochoa TJ, Clearly TG. 2004. Lactoferrin disruption of bacterial type III secretion systems. Biometals**17**(3): 257-260 CrossRef, Medline.
- Oh SM, Hahm DH, Kim IH, Choi SY. 2001. Human neutrophil lactoferrin trans-activates the matrix metalloproteinase 1 gene through stress-activated MAPK signaling modules. J. Biol. Chem.**276**(45): 42575-42579 CrossRef, Medline.
- Oh SM, Lee SH, Lee BJ, Pyo CW, Yoo NK, Lee SY, et al.. 2007. A distinct role of neutrophil lactoferrin in RelA/p65 phosphorylation on Ser536 by recruiting TNF receptor-associated factors to IκB kinase signaling complex. J. Immunol. **179**(9): 5686-5692 Medline.
- Paesano R, Berlutti F, Pietropaoli M, Pantanella F, Pacifici E, Goolsbee W, Valenti P. 2010. Lactoferrin efficacy versus ferrous sulfate in curing iron deficiency and iron deficiency anemia in pregnant women. Biometals **23**(3): 411-417 CrossRef, Medline.
- Pejler G. 1996. Lactoferrin regulates the activity of heparin proteoglycan-bound mast cell chymase: characterization of the binding of heparin to lactoferrin. Biochem. J. **320**(Pt 3): 897-903 Medline.
- Puddu P, Carollo MG, Belardelli F, Valenti P, Gessani S. 2007. Role of endogenous interferon and LPS in the immunomodulatory effects of bovine lactoferrin in murine peritoneal macrophages. J. Leukoc. Biol. **82**(2): 347-353 CrossRef, Medline.
- Puddu P, Valenti P, Gessani S. 2009. Immunomodulatory effects of lactoferrin on antigen presenting cells. Biochimie **91**(1): 11-18 CrossRef, Medline.
- Puddu P, Latorre D, Valenti P, Gessani S. 2010. Immunoregulatory role of lactoferrin-lipopolysaccharide interactions. Biometals **23**(3): 387-397 CrossRef, Medline.
- Puddu P, Latorre D, Carollo M, Catizone A, Ricci G, Valenti P, Gessani S. 2011. Bovine lactoferrin counteracts Toll-like receptor mediated activation signals in antigen presenting cells. PLoS ONE**6**(7): e22504 CrossRef, Medline.

- Qadri F, Alam MS, Nishibuchi M, Rahman T, Alam NH, Chisti J, et al.. 2003. Adaptive and inflammatory immune responses in patients infected with strains of *Vibrio parahaemolyticus*. J. Infect. Dis. **187**(7): 1085-1096 CrossRef, Medline.
- Rainard P. 1993. Activation of the classical pathway of complement by binding of bovine lactoferrin to unencapsulated *Streptococcus agalactiae*. Immunology **79**(4): 648-652 Medline.
- Reghunathan R, Jayapal M, Hsu LY, Chng HH, Tai D, Leung BP, Melendez AJ. 2005. Expression profile of immune response genes in patients with Severe Acute Respiratory Syndrome. BMC Immunol. **6**(1): 2 CrossRef, Medline.
- Rycyzyn MA, Clevenger CV. 2002. The intranuclear prolactin/cyclophilin B complex as a transcriptional inducer. Proc. Natl. Acad. Sci. U.S.A. **99**(10): 6790-6795 CrossRef, Medline.
- Samuelsen Ø, Haukland HH, Ulvatne H, Vorland LH. 2004. Anti-complement effects of lactoferrin-derived peptides. FEMS Immunol. Med. Microbiol. **41**(2): 141-148 CrossRef, Medline.
- Sasaki Y, Otsuki K, Hasegawa A, Sawada M, Chiba H, Negishi M, et al.. 2004. Preventive effect of recombinant human lactoferrin on lipopolysaccharide-induced preterm delivery in mice. Acta Obstet. Gynecol. Scand. **83**(11): 1035-1038 Medline.
- Sawatzki G, Rich IN. 1989. Lactoferrin stimulates colony stimulating factor production in vitro and in vivo. Blood Cells **15**(2): 371-385 Medline.
- Schaible UE, Collins HL, Priem F, Kaufmann SH. 2002. Correction of the iron overload defect in β-2-microglobulin knockout mice by lactoferrin abolishes their increased susceptibility to tuberculosis. J. Exp. Med. **196**(11): 1507-1513 CrossRef, Medline.
- Schwartz N. 2000. Biosynthesis and regulation of expression of proteoglycans. Front. Biosci. **5**: D649-D655 Medline.
- Sfeir RM, Dubarry M, Boyaka PN, Rautureau M, Tome D. 2004. The mode of oral bovine lactoferrin administration influences mucosal and systemic immune responses in mice. J. Nutr. **134**(2): 403-409 Medline.
- Shibata Y, Muramatsu T, Hirai M, Inui T, Kimura T, Saito H, et al.. 2002. Nuclear targeting by the growth factor midkine. Mol. Cell. Biol. **22**(19): 6788-6796 CrossRef, Medline.
- Shimamura M, Yamamoto Y, Ashino H, Oikawa T, Hazato T, Tsuda H, Iigo M. 2004. Bovine lactoferrin inhibits tumor-induced angiogenesis. Int. J. Cancer **111**(1): 111-116 CrossRef, Medline.
- Shimizu K, Matsuzawa H, Okada K, Tazume S, Dosako S, Kawasaki Y, et al.. 1996. Lactoferrin-mediated protection of the host from murine cytomegalovirus infection by a T-cell-dependent augmentation of natural killer cell activity. Arch. Virol. **141**(10): 1875-1889 CrossRef, Medline.
- Shinoda I, Takase M, Fukuwatari Y, Shimamura S, Koller M, Konig W. 1996. Effects of lactoferrin and lactoferricin on the release of interleukin 8 from human polymorphonuclear leukocytes. Biosci. Biotechnol. Biochem. **60**(3): 521-523 CrossRef, Medline.
- Siao SC, Li KJ, Hsieh SC, Wu CH, Lu MC, Tsai CY, Yu CL. 2011. Tamm-Horsfall glycoprotein enhances PMN phagocytosis by binding to cell surface-expressed lactoferrin and cathepsin G that activates MAP kinase pathway. Molecules **16**(3): 2119-2134 CrossRef, Medline.
- Smith WB, Gamble JR, Clark-Lewis I, Vadas MA. 1991. Interleukin-8 induces neutrophil transendothelial migration. Immunology **72**(1): 65-72 Medline.
- Sorimachi K, Akimoto K, Hattori Y, Ieiri T, Niwa A. 1997. Activation of macrophages by lactoferrin: secretion of TNF-α, IL-8 and NO. Biochem. Mol. Biol. Int. **43**(1): 79-87 Medline.
- Spadaro M, Caorsi C, Ceruti P, Varadhachary A, Forni G, Pericle F, Giovarelli M. 2008. Lactoferrin, a major defense protein of innate immunity, is a novel maturation factor for human dendritic cells. FASEB J. **22**(8): 2747-2757 CrossRef, Medline.
- Suzuki YA, Lönnerdal B. 2002. Characterization of mammalian receptors for lactoferrin. Biochem. Cell Biol. **80**(1): 75-80 Lien, ISI. Abstract
- Suzuki YA, Shin K, Lönnerdal B. 2001. Molecular cloning and functional expression of a human intestinal lactoferrin receptor. Biochemistry **40**(51): 15771-15779 CrossRef, Medline.
- Suzuki YA, Lopez V, Lönnerdal B. 2005. Mammalian lactoferrin receptors: structure and function. Cell. Mol. Life Sci. **62**(22): 2560-2575 CrossRef, Medline.

- Suzuki YA, Wong H, Ashida KY, Schryvers AB, Lönnerdal B. 2008. The N1 domain of human lactoferrin is required for internalization by caco-2 cells and targeting to the nucleus. Biochemistry**47**(41): 10915-10920 CrossRef, Medline.
- Szuster-Ciesielska A, Kaminska T, Kandefer-Szerszen M. 1995. Phagocytosis-enhancing effect of lactoferrin on bovine peripheral blood monocytes in vitro and in vivo. Arch. Vet. Pol. **35**(1–2): 63-71Medline.
- Takakura N, Wakabayashi H, Ishibashi H, Yamauchi K, Teraguchi S, Tamura Y, et al.. 2004. Effect of orally administered bovine lactoferrin on the immune response in the oral candidiasis murine model. J. Med. Microbiol. **53**(6): 495-500 CrossRef, Medline.
- Takayama Y, Takahashi H, Mizumachi K, Takezawa T. 2003. Low density lipoprotein receptor-related protein (LRP) is required for lactoferrin-enhanced collagen gel contractile activity of human fibroblasts. J. Biol. Chem. **278**(24): 22112-22118 CrossRef, Medline.
- Taylor KR, Gallo RL. 2006. Glycosaminoglycans and their proteoglycans: host-associated molecular patterns for initiation and modulation of inflammation. FASEB J. **20**(1): 9-22 CrossRef, Medline.
- Teegen B, Niemann S, Probst C, Schlumberger W, Stocker W, Komorowski L. 2009. DNA-bound lactoferrin is the major target for antineutrophil perinuclear cytoplasmic antibodies in ulcerative colitis. Ann. N. Y. Acad. Sci. **1173**(1): 161-165 CrossRef, Medline.
- Teng CT. 2010. Lactoferrin: the path from protein to gene. Biometals **23**(3): 359-364 CrossRef,Medline.
- Togawa J, Nagase H, Tanaka K, Inamori M, Nakajima A, Ueno N, et al.. 2002. Oral administration of lactoferrin reduces colitis in rats via modulation of the immune system and correction of cytokine imbalance. J. Gastroenterol. Hepatol. **17**(12): 1291-1298 CrossRef, Medline.
- Valenti P, Antonini G. 2005. Lactoferrin: an important host defence against microbial and viral attack. Cell. Mol. Life Sci. **62**(22): 2576-2587 CrossRef, Medline.
- van Berkel PH, Geerts ME, van Veen HA, Mericskay M, de Boer HA, Nuijens JH. 1997. N-terminal stretch Arg2, Arg3, Arg4 and Arg5 of human lactoferrin is essential for binding to heparin, bacterial lipopolysaccharide, human lysozyme and DNA. Biochem. J. **328**(1): 145-151 Medline.
- van der Does AM, Bogaards SJP, Jonk L, Wulferink M, Velders MP, Nibbering PH. 2010. The human lactoferrin-derived peptide hLF1-11 primes monocytes for an enhanced TLR-mediated immune response. Biometals **23**(3): 493-505 CrossRef, Medline.
- van Hooijdonk AC, Kussendrager KD, Steijns JM. 2000. In vivo antimicrobial and antiviral activity of components in bovine milk and colostrum involved in non-specific defence. Br. J. Nutr. **84**: S127-S134 CrossRef, Medline.
- Wakabayashi H, Takakura N, Teraguchi S, Tamura Y. 2003. Lactoferrin feeding augments peritoneal macrophage activities in mice intraperitoneally injected with inactivated *Candida albicans*. Microbiol. Immunol. **47**(1): 37-43 CrossRef, Medline.
- Wakabayashi H, Kurokawa M, Shin K, Teraguchi S, Tamura Y, Shiraki K. 2004. Oral lactoferrin prevents body weight loss and increases cytokine responses during herpes simplex virus type 1 infection of mice. Biosci. Biotechnol. Biochem. **68**(3): 537-544 CrossRef, Medline.
- Ward PP, Mendoza-Meneses M, Park PW, Conneely OM. 2008. Stimulus-dependent impairment of the neutrophil oxidative burst response in lactoferrin-deficient mice. Am. J. Pathol. **172**(4): 1019-1029 CrossRef, Medline.
- Wiesner J, Vilcinskas A. 2010. Antimicrobial peptides: the ancient arm of the human immune system. Virulence **1**(5): 440-464 CrossRef, Medline.
- Willnow TE, Goldstein JL, Orth K, Brown MS, Herz J. 1992. Low density lipoprotein receptor-related protein and gp330 bind similar ligands, including plasminogen activator-inhibitor complexes and lactoferrin, an inhibitor of chylomicron remnant clearance. J. Biol. Chem. **267**(36): 26172-26180Medline.
- Yamano E, Miyauchi M, Furusyo H, Kawazoe A, Ishikado A, Makino T, et al.. 2010. Inhibitory effects of orally administrated liposomal bovine lactoferrin on the LPS-induced osteoclastogenesis. Lab. Invest. **90**(8): 1236-1246 CrossRef, Medline.
- Yamauchi K, Wakabayashi H, Hashimoto S, Teraguchi S, Hayasawa H, Tomita M. 1998. Effects of orally administered bovine lactoferrin on the immune system of healthy volunteers. Adv. Exp. Med. Biol. **443**: 261-265 Medline.

- Yamauchi K, Wakabayashi H, Shin K, Takase M. 2006. Bovine lactoferrin: benefits and mechanism of action against infections. Biochem. Cell Biol. **84**(3): 291-296 Lien, ISI, Abstract
- Yang D, de la Rosa G, Tewary P, Oppenheim JJ. 2009. Alarmins link neutrophils and dendritic cells. Trends Immunol. **30**(11): 531-537 CrossRef, Medline.
- Yeom M, Park J, Lee B, Choi SY, Kim KS, Lee H, Hahm DH. 2011. Lactoferrin inhibits the inflammatory and angiogenic activation of bovine aortic endothelial cells. Inflamm. Res. **60**(5): 475-482 CrossRef, Medline.
- Zagulski T, Lipinski P, Zagulska A, Broniek S, Jarzabek Z. 1989. Lactoferrin can protect mice against a lethal dose of *Escherichia coli* in experimental infection in vivo. Br. J. Exp. Pathol. **70**(6): 697-704Medline.
- Zhang GH, Mann DM, Tsai CM. 1999. Neutralization of endotoxin in vitro and in vivo by a human lactoferrin-derived peptide. Infect. Immun. **67**(3): 1353-1358 Medline.
- Ziere GJ, Kruijt JK, Bijsterbosch MK, van Berkel TJ. 1996. Recognition of lactoferrin and aminopeptidase M-modified lactoferrin by the liver: involvement of proteoglycans and the remnant receptor. Biochem. J. **313**(1): 289-295 Medline.
- Zimecki M, Mazurier J, Machnicki M, Wieczorek Z, Montreuil J, Spik G. 1991. Immunostimulatory activity of lactotransferrin and maturation of CD4- CD8- murine thymocytes. Immunol. Lett. **30**(1): 119-123 CrossRef, Medline.
- Zimecki M, Mazurier J, Spik G, Kapp JA. 1995. Human lactoferrin induces phenotypic and functional changes in murine splenic B cells. Immunology **86**(1): 122-127 Medline.
- Zimecki M, Kocieba M, Kruzel M. 2002. Immunoregulatory activities of lactoferrin in the delayed type hypersensitivity in mice are mediated by a receptor with affinity to mannose. Immunobiology **205**(1): 120-131 CrossRef, Medline.
- Zimecki M, Dawiskiba J, Zawirska B, Krawczyk Z, Kruzel M. 2003. Bovine lactoferrin decreases histopathological changes in the liver and regulates cytokine production by splenocytes of obstructive jaundiced rats. Inflamm. Res. **52**(7): 305-310 Medline.
- Zimecki M, Artym J, Chodaczek G, Kocieba M, Kruzel ML. 2004. Protective effects of lactoferrin in*Escherichia coli*-induced bacteremia in mice: relationship to reduced serum TNF alpha level and increased turnover of neutrophils. Inflamm. Res. **53**(7): 292-296 CrossRef, Medline.
- Zimecki M, Artym J, Kocieba M. 2009. Endogenous steroids are responsible for lactoferrin-induced myelopoiesis in mice. Pharmacol. Rep. **61**(4): 705-710 Medline.
- Zweiman B, Kucich U, Shalit M, Von Allmen C, Moskovitz A, Weinbaum G, Atkins PC. 1990. Release of lactoferrin and elastase in human allergic skin reactions. J. Immunol. **144**(10): 3953-3960Medline.